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Modifiable risk factors for multidrug-resistant Gram-negative infection in critically ill burn patients: a systematic review and meta-analysis

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Abstract

Background: We conducted a systematic review and meta-analysis to identify potentially modifiable risk factors for multidrug-resistant Gram-negative colonization or infection in critically ill burn patients.

Methods: A systematic search was conducted of PubMed, Embase, CINAHL, Web of Science and Central (Cochrane). Risk factors including antibiotic use and hospital interventions were summarized in a random-effects meta-analysis. Risk of publication bias was assessed using the Grading of Recommendations Assessment, Development and Evaluation method and funnel plots.

Results: A total of 11 studies met the inclusion criteria. We identified several potentially modifiable risk factors and were able to grade their importance based on effect size. Related to prior antibiotic exposure, extended-spectrum cephalosporins (pooled odds ratio (OR) 7.00, 95% confidence interval (CI) 2.77–17.67), carbapenems (pooled OR 6.65, 95% CI 3.49–12.69), anti-pseudomonal penicillins (pooled OR 4.23, 95% CI 1.23–14.61) and aminoglycosides (pooled OR 4.20, 95% CI 2.10–8.39) were most significant. Related to hospital intervention, urinary catheters (pooled OR 11.76, 95% CI 5.03–27.51), arterial catheters (pooled OR 8.99, 95% CI 3.84–21.04), mechanical ventilation (pooled OR 5.49, 95% CI 2.59–11.63), central venous catheters (pooled OR 4.26, 95% CI 1.03–17.59), transfusion or blood product administration (pooled OR 4.19, 95% CI 1.48–11.89) and hydrotherapy (pooled OR 3.29, 95% CI 1.64–6.63) were most significant.

Conclusion: Prior exposure to extended-spectrum cephalosporins and carbapenems, as well as the use of urinary catheters and arterial catheters pose the greatest threat for infection or colonization with multidrug-resistant Gram-negative organisms in the critically ill burn patient population.

Introduction

Following a severe burn, 65% of deaths are caused by multisystem organ failure and, of these, infection is thought to be responsible for fatal clinical deterioration up to 46% of the time.[1] Burn patients are at high risk of infection as they characteristically experience extensive disruption to the normal protective cutaneous barrier, a decreased T-cell response, long hospital admissions, multiple surgical procedures, high rates of invasive device use and frequent health worker contact.[2] Common pathogens include: *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Enterobacter* species.[3–7] The emergence of multidrug-resistant (MDR) Gram-negative bacteria has become a serious problem in burn units because of the limited therapeutic options available and is thought to double the mortality rate from 40% to 80%.[8]

There exists a growing body of research on modifiable risk factors for MDR Gram-negative infection and colonization following burn injury.[3,4,6,7,9–17] To date, consensus on the hierarchy of modifiable risk factors has not yet been reached. Therefore, the aim of

this systematic review and meta-analysis was to synthesize existing research on potentially modifiable risk factors for MDR Gram-negative colonization or infection in the critically ill burn patient. Identifying and stratifying risk factors will help in the development of prevention strategies and improve outcomes for these patients.

Methods

This review was registered with the National Institute for Health Research international prospective register of systematic reviews 'PROSPERO' (CRD42018077827) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[18] There was no requirement for ethical approval because we analysed scientific literature already in the public domain.

Search strategy and exclusion criteria

A systematic search was conducted of PubMed, Embase, CINAHL, Web of Science and Central (Cochrane) using predefined search terms. Two researchers (MLV and GJM) independently assessed search results for inclusion based on a two-step process that screened title and abstract, and then full text. We searched from database inception to October 2017 and included only full-length peer-reviewed articles. Articles were considered for inclusion if the following criteria were met: (i) the cohort studied included exclusively burn injury patients, (ii) the study included patients in the intensive care unit (ICU) or a high acuity burn unit (burn ICU), (iii) the outcome of interest was colonization or infection with MDR Gram-negative bacteria and (iv) studies were case–control in design. The full search strategy is available in Appendix S1.

Data collection and definitions

A data extraction sheet was developed and refined during the full-text review stage. Data were independently extracted by two authors and then compared (MLV and GJM). Differences were discussed and checked for accuracy. Data were categorized as: (i) potentially modifiable risk factors, (ii) general study characteristics and (iii) author recommendations.

Modifiable risk factors were further sub-categorized into: (i) antibiotic use and (ii) hospital interventions. We considered patient demographics and burn characteristics to be non-modifiable risk factors. Antibiotic use included exposure to extended-spectrum cephalosporins, carbapenems, anti-pseudomonal penicillins, aminoglycosides, glycopeptides and fluoroquinolones. Where studies reported multiple antibiotics within a class, we collapsed the results for each class. Hospital interventions included urinary catheter use, arterial catheter use, mechanical ventilation, central venous catheter use, transfusion or blood product administration and hydrotherapy.

For general characteristics, we collected data on study type, study location, date range, cohort size, ICU population, bacteria of interest, use of molecular typing, MDR definition, outbreak status and colonization or infection status. Where studies combined data from burn wards with ICU populations, we defined the study as 'ICU and ward'. We defined 'MDR' as non-susceptibility to at least one agent in three or more classes of antibiotic as described by the joint initiative on standard definitions for acquired resistance.[19] We also considered carbapenem resistance in *A. baumannii* or *P. aeruginosa* to be MDR where a study failed to list in detail the full resistance profile. We combined the terms colonization and infection because in the literature they are often used interchangeably in this patient population.[10,17,20–23] This is because the usual physiological response to a burn involves elevated body temperature and inflammatory markers, thus making it difficult to distinguish between the two states. Where a study did not explicitly confirm outbreak status, we recorded that study as being 'non-outbreak'.

We sub-classified author recommendations as related to either antimicrobial stewardship or infection control practice. Recommendations were considered to be infection control related if they focused on surveillance, contact precautions, hygiene or isolation methods, and classified as related to antimicrobial stewardship if they suggested antibiotic de-escalation, restriction or some other change to prescribing practice.

Heterogeneity and publication bias

We reported the I^2 statistic to indicate potential heterogeneity between studies. We also conducted sensitivity analyses to elaborate on sources of potential heterogeneity by restricting to: (i) non-outbreak studies, (ii) non-colonization studies and (iii) studies conducted in high-income settings. High-income countries were identified using the World Bank classification which categorizes nations based on gross national income per capita.[24] Two researchers (MLV and GJM) independently assessed publication bias using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.[25] We considered risk of bias within four domains of potential study limitation: (i) failure to develop and apply eligibility criteria, (ii) flawed measurement of both exposure and outcome, (iii) failure to adequately control confounding and (iv) incomplete follow-up.[25] We made qualitative judgements using predefined questions and graded studies in each domain as: (i) low risk, (ii) unclear risk or (iii) high risk. A risk of bias summary was produced using RevMan 5.[26] Predefined questions and risk of bias judgements are provided in Appendix S2. The GRADE method was used in conjunction with guidance from the Cochrane Risk-of-Bias tool.[27]

Statistical analysis

We calculated unadjusted odds ratios (ORs) from colonization or infection rates provided, using a random-effects model with inverse variance weighting, which appropriately weighs the effect sizes by the inverse of the standard error of the log OR and allows for the effect to vary between studies.[28] Heterogeneity between studies was assessed using the I^2 statistic with values of 25%, 50% and 75% corresponding to low, moderate and high levels of heterogeneity, respectively. Funnel plots were used to assess risk of publication and small study bias. All analyses were performed with

RevMan (version 5) software (The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Study selection

We identified 969 PubMed, 1367 Embase, 253 CINAHL, 1024 Web of Science and 38 Central (Cochrane) publications. An additional three articles were identified from prior searches of the internet. After removal of duplicates, there were 2149 publications remaining. Author screening by title and abstract resulted in full-text review of 52 studies, of which 11 studies met all inclusion criteria. Appendix S3 details the Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow chart of the full screening process.

Study characteristics

Studies were published between 1994 and 2017 and combined data spanning from 1990 to 2015. The highest number of contributions came from France (two)[11,13] and Turkey (two),[6,12] while one study each was carried out in Australia,[15] Brazil,[9] Canada,[14] Germany,[16] Singapore,[17] Spain[4] and Taiwan.[22] Studies ran for a median of 15 months (interquartile range 12–24) and analysed a total of 289 cases from a cohort of 2221 patients. Two (18%) studies included patients from an ICU only,[15,22] two (18%) from a burn ICU[4,16] and seven (64%) combined data on ICU patients with patients from the burn ward.[6,9,11–14,17] Seven (64%) studies focused exclusively on *A. baumannii*,[6,9,11,14,16,17,22] two (18%) on *P. aeruginosa*,[12,13] one (9%) study on *K. pneumoniae*[4] and one (9%) analysed Gram-negative bacteria collectively.[15] Five (45%) studies used molecular typing to identify bacterial clones.[4,11,13,14,16] In providing a definition of MDR, eight (73%) studies listed specific antibiotics,[4,6,12–14,16,17,22] two (18%) described resistance to at least one antibiotic from three or more classes[11,15] and one (9%) referred to laboratory standards.[9] Four (36%) studies were conducted in the context of a Gram-negative outbreak,[4,11,13,14] although of the seven studies considered non-outbreak, only one specifically stated that no outbreak occurred during the study period.[15] Four (36%) studies looked at risk factors for infection,[6,13,15,16] four (36%) for colonization[9,11,12,14] and three (27%) considered colonization and infection together.[4,17,22] Recommendations to improve infection control strategies were made in seven (64%) studies,[4,6,9,12,14,16,17] while recommendations to improve antimicrobial stewardship were made in six (55%) studies.[9,11–13,22,29] Study characteristics are shown in detail in Appendix S4.

Potentially modifiable risk factors

Our meta-analysis combined data on 289 cases and 708 controls across 11 studies.[4,6,9,11–17,22] Prior antibiotic use was identified with increased odds of colonization or infection. Extended-spectrum cephalosporin exposure had the greatest effect size (pooled OR 7.00, 95% confidence interval (CI) 2.77–17.67), followed by carbapenems (pooled OR 6.65, 95% CI 3.49–12.69), anti-pseudomonal penicillins (pooled OR 4.23, 95% CI 1.23–14.61) and aminoglycosides (pooled OR 4.20, 95% CI 2.10–8.39). Of the hospital interventions included here, urinary catheter use had the greatest odds of colonization or infection (pooled OR 11.76, 95% CI 5.03–27.51), followed by arterial catheter use (pooled OR 8.99, 95% CI 3.84–21.04), mechanical ventilation (pooled OR 5.49, 95% CI 2.59–11.63), central venous catheter use (pooled OR 4.26, 95% CI 1.03–17.59), transfusion or blood product administration (pooled OR 4.19, 95% CI 1.48–11.89) and hydrotherapy (pooled OR 3.29, 95% CI 1.64–6.63). Pooled OR for potentially modifiable risk factors are provided in Table 1.

Heterogeneity and publication bias

The I^2 statistic varied from 0% to 87% for antibiotic use pooled estimates and from 0% to 82% for hospital intervention estimates, indicating none to very high heterogeneity between studies (Appendices S5,S6). Funnel plots were generated to determine evidence of bias for studies assessing antibiotic use and hospital interventions. Interpretation of funnel plots indicates an overall acceptable distribution.

Table 1 Pooled effect sizes and 95% CI of multidrug-resistant Gram-negative colonization or infection in critically ill burn patients according to antibiotic use and hospital interventions

Potentially modifiable risk factors	Studies	Number of cases	Number of controls	Pooled OR (95% CI)
Antibiotic use				
Extended-spectrum cephalosporin†	6, 9, 12–17	103/227	70/573	7.00 (2.77–17.67)
Carbapenem‡	6, 9, 12, 13, 15, 17	60/169	26/428	6.65 (3.49–12.69)
Anti-pseudomonal penicillin§	6, 9, 12, 13, 15, 17	55/164	53/443	4.23 (1.23–14.61)
Aminoglycoside¶	6, 9, 12–17	102/227	83/573	4.20 (2.10–8.39)
Glycopeptide††	6, 9, 12, 13, 15, 17	47/169	82/428	2.00 (0.43–9.41)
Fluoroquinolone‡‡	9, 12, 13, 15, 17	24/139	29/368	1.82 (0.74–4.48)
Hospital interventions				
Urinary catheter	9, 13, 16, 17	92/107	108/312	11.76 (5.03–27.51)
Arterial catheter	13, 14, 16	66/73	85/177	8.99 (3.84–21.04)
Mechanical ventilation	4, 9, 11, 13, 14, 16, 22	122/162	158/491	5.49 (2.59–11.63)
Central venous catheter	4, 9, 13, 14, 16	96/128	147/376	4.26 (1.03–17.59)
Transfusion/blood products	6, 9, 14	44/88	55/326	4.19 (1.48–11.89)
Hydrotherapy	14, 16	39/58	55/145	3.29 (1.64–6.63)

†Cefotaxime, ceftriaxone, ceftazidime and cefepime. ‡Irtapenem, imipenem, meropenem and doripenem. §Piperacillin-tazobactam and ticacillin-clavulanate. ¶Gentamicin, tobramycin, amikacin and netilmicin. ††Vancomycin, teicoplanin and telavancin. ‡‡Ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and pefloxacin. CI, confidence interval; OR, odds ratio.

Funnel plots are shown in Appendix S7. Sensitivity analyses restricted to the seven non-outbreak studies,[6,9,12,15–17,22] and seven non-colonization studies[4,6,13,15–17,22] showed little change to the risk estimates. Sensitivity analysis for the seven high-income countries (Taiwan, France, Spain, Canada, Australia, Singapore and Germany)[4,11,13–17,22] showed little change for hospital interventions and some change for antibiotic use. With studies from lower income countries removed,[6,9,12] the I^2 statistic varied from 0% to 79% for antibiotic use and the hierarchy of antibiotics shifted. In order of decreasing effect size, our high-income country sensitivity analysis identified the following significant antibiotic exposures: carbapenems (pooled OR 4.51, 95% CI 1.87–10.90), aminoglycosides (pooled OR 3.77, 95% CI 1.07–13.34) and extended-spectrum cephalosporins (pooled OR 3.6, 95% CI 1.52–8.52). Using the GRADE method, we found the overall risk of bias to be low. Three studies were considered unclear risk for measure of exposure and outcome because they combined results for colonization and infection,[4,17,22] while two studies were also considered unclear risk for control of confounding because they were based on small groups of young adults or children.[6,22]

Discussion

We conducted this study in order to identify potentially modifiable risk factors for MDR Gram-negative bacterial colonization or infection among critically ill burn patients. We categorized potentially modifiable risk factors as related to either antibiotic use or hospital interventions.

For antibiotic use, we found that exposure to any of the following antibiotic classes between admission and MDR bacterial isolation was significant: extended-spectrum cephalosporins, carbapenems, aminoglycosides and anti-pseudomonal penicillins. It is well understood that antibiotic pressures drive the acquisition of MDR mechanisms in Gram-negative bacteria.[11,20,30] Laboratory studies have demonstrated that common burn pathogens such as *P. aeruginosa* and *A. baumannii* predictably progress to MDR status following exposure to inadequate minimum inhibitory concentrations of some classes of antibiotics.[10–13,15,22] Burn wounds are rapidly colonized by endogenous and exogenous bacteria during the post-injury days and are thought to provide the ideal environment for resistance emergence because systemic antibiotics are less likely to penetrate the poorly vascularized tissue.[3,6,13,20,31] In addition to directly selecting for resistance, antibiotics are also thought to confound the problem of horizontal transmission by eradicating normal regulatory flora and thereby facilitating colonization by resistant bacteria in otherwise previously unexposed patients.

All of the hospital interventions assessed were statistically significant and in order of decreasing effect size these included: urinary catheters, arterial catheters, mechanical ventilation, central venous lines, blood or blood product administration and hydrotherapy. Even with strict isolation and infection control practices, the horizontal transmission of bacteria between human reservoirs occurs continuously in the ICU.[4,12,14,30] Our finding regarding urinary catheters, intravascular lines and mechanical ventilation likely reflects the role of these devices as portals of entry for exogenously acquired MDR Gram-negative bacteria.[4,16,17] Hydrotherapy equipment is also well known to increase horizontal transmission of burn wound pathogens and has been phased out in many burn centres for this reason.[13,16] Wong *et al.* state that higher rates of intervention should also be considered a surrogate for illness severity and thus increased frequency of health worker contact.[17] Studies included here that used molecular typing emphasize the importance of horizontal transmission. Sanchez *et al.* and Munier *et al.* used typing techniques to demonstrate that a single clone was responsible for all MDR cases during their study periods.[4,11] While in a non-outbreak situation, Wisplinghoff *et al.* found just three clones and suggested that among their cases MDR pathogens were also likely to be largely acquired horizontally.[16]

Strengths and limitations

Two reviewers independently reviewed all titles, abstracts and full-text publications to ensure the final data set included a homogeneous cohort of patients. We also performed three sets of sensitivity analyses, within non-outbreak studies, non-colonization studies and high-income countries. All three made little change to the pooled effect sizes and this confirms the robustness of our findings.

Several limitations existed that may have impacted our findings. First, there was inconsistency in the use of a standard definition for MDR. A universal definition of MDR would greatly facilitate understanding between researchers and we recommend the proposal by Magiorakos *et al.* which provides species-specific criteria and defines MDR as non-susceptibility to at least one agent in three or more classes of antibiotic.[19] Second, we found that not all studies explicitly confirmed outbreak status and no studies defined a definition for 'outbreak'. We attempted to mitigate for this through sensitivity analysis; removal of studies that used the term outbreak found little impact on pooled effect sizes. And finally, we found that when performing sensitivity analysis of studies from high-income countries, there was some shift to the hierarchy of antibiotic risk factors. We could not control for this effect, although three of the four significant antibiotic classes identified in our meta-analysis were also significant classes in our sensitivity analysis.

Conclusion

The most important modifiable risk factors associated with an increased risk of colonization or infection with an MDR Gram-negative bacteria in the critically ill burn patient include prior exposure to extended-spectrum cephalosporins or carbapenems and the use of urinary or arterial catheters.

Conflicts of interest

None declared.

References

1. Bloemsma GC, Dokter J, Boxma H, Oen IM. Mortality and causes of death in a burn centre. *Burns* 2008; **34**: 1103–7.
2. van Langeveld I, Gagnon RC, Conrad PF *et al.* Multiple-drug resistance in burn patients: a retrospective study on the impact of antibiotic

resistance on survival and length of stay. *J. Burn Care Res.* 2017; **38**: 99–105.
3. Alp E, Coruh A, Gunay GK, Yontar Y, Doganay M. Risk factors for nosocomial infection and mortality in burn patients: 10 years of experience at a university hospital. *J. Burn Care Res.* 2012; **33**: 379–85.
4. Sanchez M, Herruzo R, Marban A *et al*. Risk factors for outbreaks of multidrug-resistant *Klebsiella pneumoniae* in critical burn patients. *J. Burn Care Res.* 2012; **33**: 386–92.
5. Sun FJ, Zhang XB, Fang Y *et al*. Spectrum and drug resistance of pathogens from patients with burns. *Burns* 2012; **38**: 1124–30.
6. Tekin R, Dal T, Bozkurt F *et al*. Risk factors for nosocomial burn wound infection caused by multidrug resistant *Acinetobacter baumannii*. *J. Burn Care Res.* 2014; **35**: e73–80.
7. Azzopardi EA, Azzopardi E, Camilleri L *et al*. Gram negative wound infection in hospitalised adult burn patients – systematic review and metanalysis. *PLoS One* 2014; **9**: e95042.
8. Williams FN, Herndon DN, Hawkins HK *et al*. The leading causes of death after burn injury in a single pediatric burn center. *Crit. Care* 2009; **13**: R183.
9. Cavalcante Rde S, Canet P, Fortaleza CM. Risk factors for the acquisition of imipenem-resistant *Acinetobacter baumannii* in a burn unit: an appraisal of the effect of colonization pressure. *Scand. J. Infect. Dis.* 2014; **46**: 593–8.
10. Messadi AA, Lamia T, Kamel B, Salima O, Monia M, Saida BR. Association between antibiotic use and changes in susceptibility patterns of *Pseudomonas aeruginosa* in an intensive care burn unit: a 5-year study, 2000-2004. *Burns* 2008; **34**: 1098–102.
11. Munier AL, Biard L, Rousseau C *et al*. Incidence, risk factors, and outcome of multidrug-resistant *Acinetobacter baumannii* acquisition during an outbreak in a burns unit. *J. Hosp. Infect.* 2017; **97**: 226–33.
12. Ozkurt Z, Ertek M, Erol S, Altoparlak U, Akcay MN. The risk factors for acquisition of imipenem-resistant *Pseudomonas aeruginosa* in the burn unit. *Burns* 2005; **31**: 870–3.
13. Richard P, Le Floch R, Chamoux C, Pannier M, Espaze E, Richet H. *Pseudomonas aeruginosa* outbreak in a burn unit: role of antimicrobials in the emergence of multiply resistant strains. *J. Infect. Dis.* 1994; **170**: 377–83.
14. Simor AE, Lee M, Vearncombe M *et al*. An outbreak due to multiresistant *Acinetobacter baumannii* in a burn unit: risk factors for acquisition and management. *Infect. Control Hosp. Epidemiol.* 2002; **23**: 261–7.
15. Vickers ML, Dulhunty JM, Ballard E *et al*. Risk factors for multidrug-resistant Gram-negative infection in burn patients. *ANZ J. Surg.* 2018; **88**: 480–5.
16. Wisplinghoff H, Perbix W, Seifert H. Risk factors for nosocomial bloodstream infections due to *Acinetobacter baumannii*: a case-control study of adult burn patients. *Clin. Infect. Dis.* 1999; **28**: 59–66.
17. Wong TH, Tan BH, Ling ML, Song C. Multi-resistant *Acinetobacter baumannii* on a burns unit – clinical risk factors and prognosis. *Burns* 2002; **28**: 349–57.
18. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int. J. Surg.* 2010; **8**: 336–41.
19. Magiorakos AP, Srinivasan A, Carey RB *et al*. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin. Microbiol. Infect.* 2012; **18**: 268–81.
20. Friedstat JS, Moore ME, Weber JM, Fagan SP, Goverman J. Selection of appropriate empiric gram-negative coverage in a multinational pediatric burn hospital. *J. Burn Care Res.* 2013; **34**: 203–10.
21. Ho AL, Chambers R, Malic C, Papp A. Universal contact precautions do not change the prevalence of antibiotic resistant organisms in a tertiary burn unit. *Burns* 2017; **43**: 265–72.
22. Huang PY, Shie SS, Ye JJ *et al*. Acquisition and clearance of multidrug resistant *Acinetobacter baumannii* on healthy young adults concurrently burned in a dust explosion in Taiwan: the implication for antimicrobial stewardship. *BMC Infect. Dis.* 2017; **17**: 598.
23. Thabet L, Memmi M, Turki A, Messadi AA. The impact of fluoroquinolones use on antibiotic resistance in an intensive care burn department. *Tunis. Med.* 2010; **88**: 696–9.
24. worldbank.org. The World Bank Country and Lending Groups. 2018. [Cited 1 Oct 2018.] Available from URL: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups
25. Guyatt GH, Oxman AD, Vist G *et al*. GRADE guidelines: 4. Rating the quality of evidence – study limitations (risk of bias). *J. Clin. Epidemiol.* 2011; **64**: 407–15.
26. Review Manager (Revman). Computer program. Version 5.3. Copenhagen: The Nordic Cochrane Centre TCC, 2014.
27. Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester and Hoboken, NJ: John Wiley & Sons, 2008.
28. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp. Clin. Trials* 2007; **28**: 105–14.
29. Mahar P, Padiglione AA, Cleland H, Paul E, Hinrichs M, Wasiak J. *Pseudomonas aeruginosa* bacteraemia in burns patients: risk factors and outcomes. *Burns* 2010; **36**: 1228–33.
30. Ferreira AC, Gobara S, Costa SE *et al*. Emergence of resistance in *Pseudomonas aeruginosa* and Acinetobacter species after the use of antimicrobials for burned patients. *Infect. Control Hosp. Epidemiol.* 2004; **25**: 868–72.
31. Fadeyibi IO, Raji MA, Ibrahim NA, Ugburo AO, Ademiluyi S. Bacteriology of infected burn wounds in the burn wards of a teaching hospital in Southwest Nigeria. *Burns* 2013; **39**: 168–73.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Full search strategy.
Appendix S2. Risk of bias assessment.
Appendix S3. PRISMA flow diagram of study selection.
Appendix S4. Study characteristics.
Appendix S5. Forest plots of pooled odds ratios for multidrug-resistant Gram-negative colonization or infection in critically ill burn patients according to antibiotic use.
Appendix S6. Forest plots of pooled odds ratios for multidrug-resistant Gram-negative colonization or infection in critically ill burn patients according to hospital interventions.
Appendix S7. Funnel plots of studies combined to analyse potentially modifiable antibiotic use and hospital interventions.