CRITICAL CARE

REVIEW

Year in review 2011: *Critical Care* – infection

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Abstract

There is an ever-growing importance for critical assessment of benefits and harms of various strategies with regards to antibiotic stewardship, infection control, molecular detection of pathogens and adequate treatment of multidrug-resistant organisms in ICUs. Ongoing financial constraints globally, changing demographics with an increasing and aging population and the slow introduction of new antibiotics make the utilisation of the best available evidence and goal-directed strategies essential in the ICU setting. This review will summarise findings from some of the recent major publications in the area of infectious diseases with emphasis on the role of behaviour change strategies for infection control purposes, the role of biomarkers such as C-reactive protein and procalcitonin, and the impact of molecular diagnostics in clinical decision-making. Furthermore, we will update readers on some recent findings in relation to invasive fungal infections, community-acquired pneumonia and ventilator-associated pneumonia in ICU patients.

Introduction

Despite continuous awareness and ongoing efforts to combat infections among critically ill patients, infection still remains a growing challenge and consumes a substantial amount of resources. Infection prevention and control through early detection of pathogens, initiation of rational and appropriate antimicrobial stewardship and reduction of healthcare-associated infections remains one of the essential goals in our daily management of critically ill patients. This paper will provide a snapshot overview of a selected subset of recent publications across various journals pertinent to critical care, clinical infectious diseases and infection control during the last 12 months with a special aim at patients hospitalised in ICUs.

Behaviour change strategies for antibiotic stewardship and infection control

Beyond the traditional antibiotic stewardship approaches, there is an increasing awareness of other equally important contributing factors such as the role of behaviour change strategies to influence antibiotic prescribing in critical care. To assess the latter, Charani and colleagues included five qualitative and five quantitative studies in a systematic review; the qualitative studies placed emphasis on the predominant influence of social norms, cultures and attitudes on antimicrobial prescribing, while the quantitative studies focused on optimisation of antimicrobial prescribing behaviour [1]. The latter is influenced by various determinants: cultural beliefs of the patient and the prescriber, and behavioural and contextual determinants such as socioeconomic issues, the need for autonomy in the clinical decision-making process, professional relationships and medical hierarchy [2-4].

These variables may ultimately result in different practices locally, nationally or internationally. The authors found an overall poor quality of the interventions applied to optimise prescribing behaviour and recommend more targeted research to ensure a greater appreciation of prescribing behaviour while improving the quality of interventions in a multidisciplinary setting.

In a systematic review, Edwards and colleagues assessed the effectiveness and sustainability of various interventions for changing infection control behaviour, with barriers towards and facilitators of behaviour change [5]. They included seven interventional and 14 exploratory studies that all led to behaviour change, reduced infection rate or both, but no intervention study incorporated psychological theory while two addressed social marketing in design and five assessed sustainability. Most infection-prevention papers did not meet the quality criteria, indicating an early stage of such research. Only a limited number of studies incorporated psychological or social marketing methods for behaviour change, despite assessing sustainability. Overall, very few studies applied robust methodology. More interventional studies are required to improve behaviour change strategies in infection control.

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Biomarkers

In a prospective cohort study of 191 patients with severe community-acquired pneumonia (CAP) requiring ICU admission, Coelho and colleagues examined the value of different patterns of C-reactive protein (CRP)-ratio response to antibiotic therapy [6]. After CRP sampling every other day until day 7 of antibiotic therapy, the CRP ratio was calculated in relation to the day 1 concentration. The authors found a more rapid decrease in the CRP ratio among survivors than among nonsurvivors ($P = 0.01$) and they found an ability of the CRP ratio to predict ICU mortality at day 5 assessed by an area under the receiver operating characteristic curve of 0.73 (95% confidence interval (CI), 0.64 to 0.82). The ICU mortality rate varied significantly among different groups, with the individual pattern of the CRP ratio defined as fast response (4.8%), slow response (17.3%) and nonresponse (36.4%) ($P < 0.001$). Serial evaluation of the CRP ratio may be a valuable tool for early detection of patients with severe CAP who are at risk of poor outcome.

Numerous recent publications have assessed the application of algorithms based on procalcitonin (PCT) as a rapid-reacting biomarker of bacterial infection for antibiotic stewardship. In a recent multicentre randomised controlled trial (RCT), Jensen and colleagues randomised 1,200 critically ill patients to either a standard clinical judgement arm (blinded to PCT levels) or a PCT-guided treatment arm with a mandatory drug-escalation algorithm and antimicrobial guidance based on daily PCT measurements [7]. They failed to show any benefit on all-cause 28-day mortality in the PCT arm (31.5%, 190 of 604) compared with the control arm (32.0%, 191 of 596). More disappointingly, the length of the ICU stay increased by 1 day in the PCT arm ($P = 0.004$) and there was an indication of organ-related harm (kidney injury). The rate of mechanical ventilation also increased by 4.9% (95% CI, 3.0 to 6.7%). There was a substantially higher use of broad-spectrum antimicrobials in the PCT arm without an earlier appropriate choice of antimicrobial treatment, except among those patients with proven bloodstream infection (BSI). There was a higher frequency of microbiologic sampling in the PCT arm, mainly due to more airway and urine samples and blood culture (BC). This study's findings somewhat contradicts the recent systematic reviews, which despite no indication of improved mortality (Figure 1) showed benefits among patients with respiratory tract infection and sepsis by significantly reducing antibiotic exposure and showed a trend towards reduced costs and reduced length of ICU stay [8-12].

Impact of molecular diagnostics on clinical decision-making

Molecular diagnostics play an increasing role in pathogen detection in critically ill patients, which could ultimately improve antibiotic stewardship and clinical outcomes [13]. Frye and colleagues assessed the impact of real-time PCR, reporting on timely identification of clustered Gram-positive cocci in BCs and on the appropriate choice of antimicrobial treatment [14]. In this retrospective study, patients with *Staphylococcus aureus* bacteraemia were compared in a 12-month pre-PCR period ($n = 68$) and in a 12-month PCR implementation period ($n = 58$) with the BD-GeneOhm-StaphSR assay (BD-GeneOhm, CA, USA). The investigators used similar numbers of consecutive patients with coagulase-negative staphylococci as comparison. They found a significantly reduced time to identification during the PCR period (mean 34.1 vs. 47.3 hours; $P < 0.0001$) but no significant reduction in time to optimal antibiotic therapy. Nevertheless, the implementation of a PCR assay may not only lead to a more rapid microbiological identification but also reduce the unnecessary use of vancomycin in methicillin-susceptible *S. aureus* and clinically insignificant coagulase-negative staphylococcal infections. The full potential of PCR methods can only be achieved when they are able to provide clinicians with rapid and reliable information [15-17].

SeptiFast (Roche, Germany) remains the most thoroughly examined PCR multiplex platform for rapid diagnosis of BSI. Pasqualini and colleagues examined this platform's diagnostic accuracy and clinical usefulness in 391 adult patients with suspected sepsis in comparison with BC [18]. In 22% of patients a causative pathogen was detected, among which 60 pathogens were identified by SeptiFast and 57 pathogens by BC. SeptiFast false-negative samples were interpreted as caused by various factors such as low microbial load (especially for coagulase-negative staphylococci), low sample volume, inappropriate sample preparation procedures or genetic variability. There was no significant difference between the two methods in the rates of pathogen detection even when excluding pathogens solely isolated by BC. However, the combination of BC and SeptiFast significantly increased the detection rate in comparison with BC alone. Additionally, SeptiFast had a significantly lower contamination rate (0 vs. 19 cases in BC), a higher specificity for pathogen detection (1.00 vs. 0.94; $P = 0.005$) and a higher positive predictive value than BC (1.00 vs. 0.75; $P = 0.005$). Interestingly, the authors detected more pathogens (16 versus 6; $P = 0.049$) with SeptiFast in the 191 antibiotic-pretreated patients compared with BC. The results of this study further confirm a role for molecular technologies as an adjunct to BC, especially among antibiotic-pretreated ICU patients [13].

Beyond the scope of improved treatment, rapid molecular diagnostic tests have the potential to decrease the cost of ICU patient care related to preemptive use of contact precautions. Wassenberg and colleagues

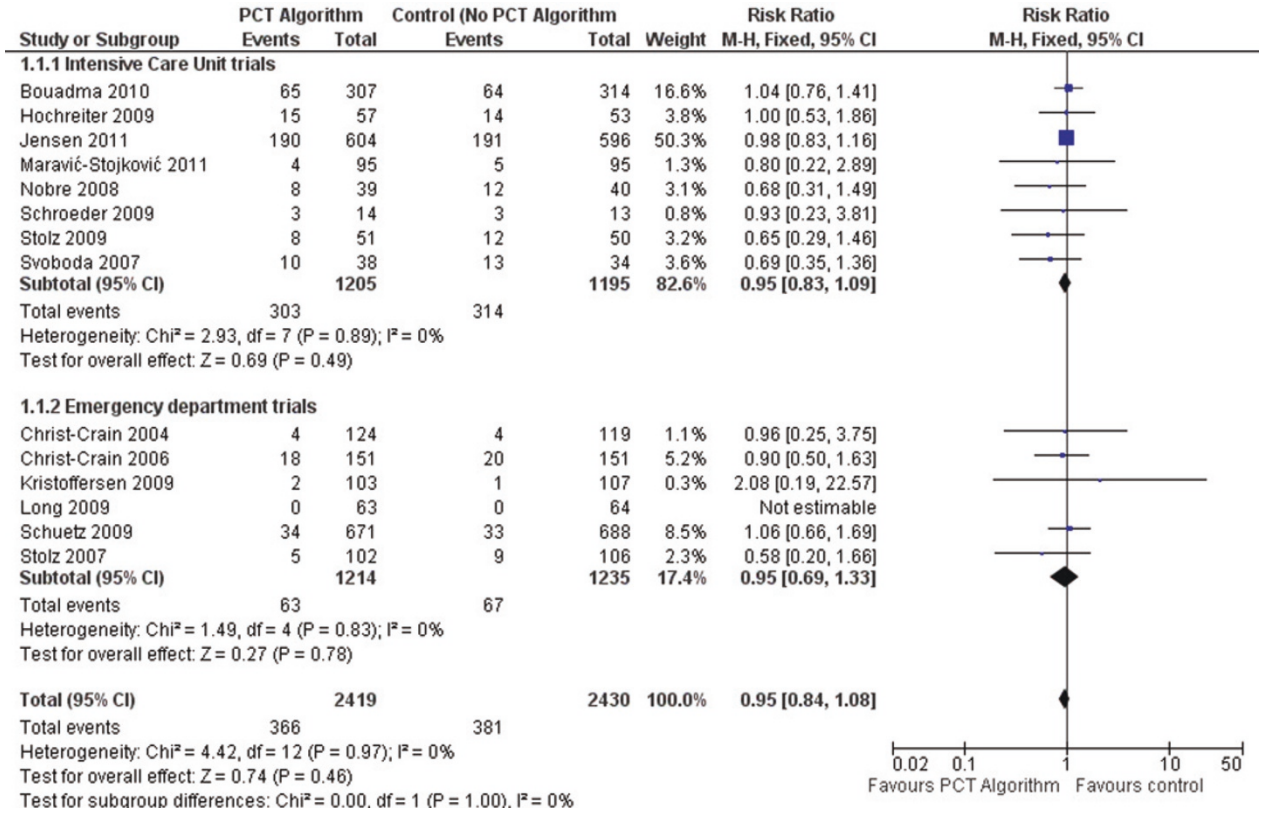

Figure 1. Updated meta-analytic assessment of mortality with procalcitonin-guided treatment versus control. CI, confidence interval; M-H, Mantel-Haenszel test; PCT, procalcitonin.

examined the costs and benefits of rapid screening of methicillin-resistant *S. aureus* (MRSA) carriage in ICUs [19]. In this multicentre Dutch study, BD GeneOhm™ MRSA-PCR (GeneOhm, CA, USA) and GeneXpert-MRSA (Cepheid, CA, USA) were compared with culture results as reference. MRSA prevalence was reported at 3.1% among 163 patients at risk of carriage. The authors reported a negative predictive value of 100% for both PCR methods and the duration of patient isolation as 27.6 hours for GeneOhm and 21.4 hours for GeneXpert, while using cultures as reference would have resulted in 96-hour isolation. There was a 44.3% reduction in isolation days with the PCR screening at the additional cost per patient screened of €327.84 (GeneOhm) and €252.14 (GeneXpert). This resulted in a net saving of €136.04 (GeneOhm) and €121.76 (GeneXpert) per isolation day avoided. The reduction in isolation was less than previously reported values for general wards (54 to 60%) and perhaps reflects the complexities of ICU patients with multiple sites to be screened (i.e., intravenous lines, multiple wounds, catheters) [20,21]. Additionally, most of the current molecular platforms are unable to examine multiple tests in a short period of time. To reduce the duration of costly and often difficult preemptive isolation of high-risk patients, technical improvement of molecular diagnostics and strategies such as pooling of swabs are therefore required to cope with large-volume testing.

Severe pneumonia in the ICU

Ventilator-associated pneumonia (VAP) remains the second leading cause of nosocomial infections in ICUs, associated with increased adverse outcomes and economic costs [22]. Melsen and colleagues assessed the attributable mortality of VAP using data from 58 RCTs on VAP prevention, and estimated an attributable mortality rate of 9% (range, 3 to 17%) [23]. The impact of ureido/carboxypenicillin resistance on the prognosis of VAP with *Pseudomonas aeruginosa* was studied by Kaminski and colleagues in a retrospective study of 223 cases [24]. There was more frequent delay in the initiation of adequate antimicrobial treatment among patients with resistance to ureido/carboxypenicillin but no difference in ICU or hospital mortality after adjustment among those patients with resistance. Mortality also remained unaltered among the subset of patients receiving adequate antimicrobial treatment for VAP on the day of diagnosis.

The proportion of polymicrobial aetiology and its impact on survival vary in the literature [25,26]. In a prospective observational study, Cillóniz and colleagues provided data on prevalence, clinical characteristics and outcome of 362 consecutive adult patients with severe CAP admitted to ICUs within 24 hours of symptom debut [27]. They established the CAP aetiology in 54% (n = 196) of patients. Monomicrobial infection was detected in 43% (n = 157) while 11% (n = 39) were categorised as polymicrobial (two pathogens, n = 33; three pathogens, n = 6). Patients with polymicrobial infection were found to have a greater degree of inappropriate initial antimicrobial therapy (39% vs. 10%; $P < 0.001$), a more severe clinical picture with confounding conditions such as acute respiratory distress syndrome and septic shock, and a nonsignificant increase in mortality (21% vs. 11%, n = 8 vs. 17; P = 0.10). *Streptococcus pneumoniae* was the most prevalent pathogen (72%, n = 28), followed by respiratory viruses (39%, n = 15) and *P. aeruginosa* (21%, n = 8). Inappropriate initial antibiotic was an independent predictor of in-hospital mortality (odds ratio = 10.8). However, limitations such as a lack of complete microbiological sampling, a large proportion of antibiotic-pretreated patients (21%) and no application of molecular techniques may impair the true validity of these findings. Other frequently identified pathogens in the two-pathogen group and in the polymicrobial group were MRSA, *P. aeruginosa*, Gram-negative enteric bacilli (that is, *Escherichia coli*, *Klebsiella pneumoniae*, *Serratia marcescens*), *Haemophilus influenza* and *Moraxella catarrhalis*. The most commonly detected viruses across all groups were Influenza A and *Legionella pneumophila*.

New insights into antibiotic treatment modalities and agents

According to recent data, BSI occurs in about 15% of ICU patients and is associated with increased mortality and morbidity [28]. Optimisation of the antimicrobial treatment duration for BSI could potentially reduce antibiotic utilisation, resistance, costs and adverse events. In a systematic review, Havey and colleagues assessed this issue by including 24 studies (one RCT) [29]. Overall, the authors found little evidence to suggest an optimal duration of treatment for BSI while data from subgroup analyses of various RCTs have suggested equal benefit from shorter duration of therapy (<8 days) compared with longer-duration therapy regarding morbidity, mortality or microbiological cure. The authors also highlight the potential importance of having a longer duration of treatment for *S. aureus* bacteraemia and thus consider it separately from other pathogens. There was very limited evidence to guide optimal treatment of catheter-related BSI, VAP, CAP, pyelonephritis and intraabdominal infections in ICU patients [29]. The decision on the duration of therapy should thus currently be based on the clinical response rather than a specific time interval because it is difficult to account for the vast number of variables influencing treatment efficacy.

In another systematic review, Gonçalves-Pereira and Póvoa examined the pharmacokinetics of six different β-lactam antibiotics (meropenem, imipenem, piperacillin, cefpirome, cefepime and ceftazidime) in septic ICU patients [30]. The authors included 57 studies and found significant pharmacokinetics heterogeneity with more than twofold variation in both the volume of distribution and drug clearance. They found the β-lactam half-life and the time in which the drug concentration exceeds the bacteria minimal inhibitory concentration (MIC) to be quite unpredictable. Despite a better pharmacodynamic profile with more frequent dosing and prolonged or continuous infusions, whether this actually translates into improved survival or reduced emergence of resistance remains to be shown. Nevertheless, therapeutic drug monitoring of the β-lactam antibiotic concentration among ICU patients could potentially improve efficacy, prevent toxicity and ultimately improve clinical outcomes [31].

Tigecycline, the first representative of the glycycline class, has reported activity against a wide range of pathogens. Tasina and colleagues examined the efficacy of tigecycline for the treatment of adult patients with bacterial infection by conducting a systematic review of 14 RCTs, including 7,400 patients [32]. Interestingly, the authors found nonsignificantly lower success rates with tigecycline than with control antibiotics, with a more frequent rate of adverse events in the tigecycline group (odds ratio = 1.45; 95% CI, 1.11 to 1.88). They also found a nonsignificant trend towards higher all-cause mortality in the tigecycline group (odds ratio = 1.28; 95% CI, 0.97 to 1.69). Another recent systematic review pooling non-inferiority RCTs of serious infections found an increased overall mortality (0.7% absolute or 30% relative risk increase) associated with tigecycline therapy independent of type of infection or comparator antibiotic regimen [33]. There is thus currently little evidence to support a superiority of tigecycline against standard antimicrobials for treatment of serious infections. In particular, tigecycline should be avoided for the treatment of severe pneumonia in critically ill patients.

Emergence of multidrug-resistant organisms has revitalised colistin, a polymyxin antimicrobial potentially useful for treatment of multidrug-resistant pathogens such as *P. aeruginosa*, *Acinetobacter baumannii* and carbapenem-resistant *Enterobacteriaceae*. Although colistin retains *in vitro* activity against most of these Gram-negative pathogens, it is crucial to preserve its activity as a last-line drug while also minimising the

potential for adverse effects. In a retrospective cohort study of all patients receiving colisitin for ≥48 hours over a 5-year period, Pogue and colleagues raise important safety concerns by reporting a 43% (n = 54) colistin-associated nephrotoxicity [34]. Nephrotoxicity occurred in a dose-dependent manner, with higher mean colistin doses significantly increasing the risk (5.48 vs. 3.95 mg/kg/day; P <0.001). Nephrotoxicity was reported at doses lower than currently recommended in the United States (higher than European guidelines), with 30% among those receiving between 3.0 and 4.9 mg/kg/day based on ideal body weight but reaching as high as 69% when doses exceeded 5.0 mg/kg/day. One major cause for concern is that the dosing in many institutions is based on actual body weight and not ideal body weight, which may put a substantial number of patients at risk of exceeding the 5.0 mg/kg/day for ideal body weight. Time-averaged exposure appears to be important for colistin bactericidal activity, and therefore the currently used dosage regimens of colistin methan-sulfonate – the inactive prodrug in equilibrium with colistin active form – could generate suboptimal therapeutic exposure, especially in critically ill patients. The identification of the area under the curve/time to MIC ratio as the major efficacy determinant may help tailor optimal dosage regimens in the near future [35].

Florescu and colleagues looked at the efficacy and safety of intravenous and aerosolised forms of colistin for VAP treatment in a systematic review by including six RCTs (359 patients) and 14 observational studies (437 patients) [36]. They found no significant difference between colisitin and controls with respect to mortality, length of ICU stay or nephrotoxicity. These findings did not change after adjusting for concomitant antibiotic treatment and the route of colistin administration. The sample size of this meta-analysis was inadequate, however, and there was a significant difference in the mean dose of colistin used in aerosolised form.

In a double-blind multicentre RCT, Wunderink and colleagues assessed the efficacy and safety of linezolid compared with a dose-optimised vancomycin strategy against MRSA nosocomial pneumonia in 448 adult participants [37]. Patients were randomised to either intravenous linezolid (600 mg every 12 hours) or vancomycin (15 mg/kg every 12 hours) for 7 to 14 days with continuous dose adjustment of vancomycin. Clinical success was achieved at the end of the study in 57.6% of the linezolid group versus 46.6% of the vancomycin group (95% CI for difference, 0.5 to 21.6%; P = 0.042). There was similar all-cause mortality at 60 days (linezolid, 15.7% vs. vancomycin, 17.0%) while renal toxicity occurred more frequently with vancomycin (18.2% vs. linezolid, 8.4%). There was a similar rate of adverse events in both groups and there was no difference with regards to mortality from MRSA pneumonia. However, patients were allowed up to 48 hours of vancomycin treatment prior to randomisation, which could favour the linezolid group. Furthermore, one could argue that it would be hard to carry out adequate blinding when vancomycin should be given over 90 to 120 minutes whereas linezolid can be administered in 15 to 30 minutes. Finally, one should also consider the impact of conflict of interest and funding bias in this industry-designed and sponsored trial. The findings of this study contradict the conclusions of a recently published systematic review by Walkey and colleagues in which the authors found no superiority of linezolid over glycopeptide antibiotics [38]. By including the results of Wunderink and colleagues in various relevant meta-analyses, despite trends towards improved microbiological and clinical success and improved survival, these findings are still statistically nonsignificant and therefore more studies are needed (Figure 2).

Fungal infections

Invasive fungal infections, notably invasive aspergillosis and candidaemia, are still a major challenge in ICUs. Some new insights about invasive aspergillosis in ICU patients were presented last year [31], and important papers have been recently published about the management of candidaemia in critically ill patients. Hermsen and colleagues conducted a retrospective matched case–control study in the ICU of a Nebraska academic medical centre to validate and compare two clinical prediction rules (Paphitou and Ostrosky-Zeichner) aimed at identifying patients who may benefit from antifungal prophylaxis or early empiric therapy [39]. They found an incidence of 2.3% for invasive candidiasis among 352 adult patients with an ICU stay of at least 4 days, and both prediction rules exhibited similar performance in identifying low-risk patients who are not likely to develop invasive candidiasis, based on high negative predictive values.

Muskett and colleagues performed a systematic review of risk factors for invasive fungal disease in critically ill patients [40]. Surgery, total parenteral nutrition, fungal colonisation, renal replacement therapy and sepsis were found, among others, to be significantly associated with invasive fungal infections. Taken together, these approaches could be helpful for preventing unnecessary antifungal use and optimising patient care.

However, candidaemia remains an invasive infection with a crude mortality exceeding 50% [41]. The importance of first-line antifungal agents has been evaluated in two important papers yielding concurrent results. In particular, Ha and colleagues found that treatment failure of first-line antifungal agents was one of the most important risk factors for mortality among ICU patients with candidaemia in four tertiary-care hospitals in Korea

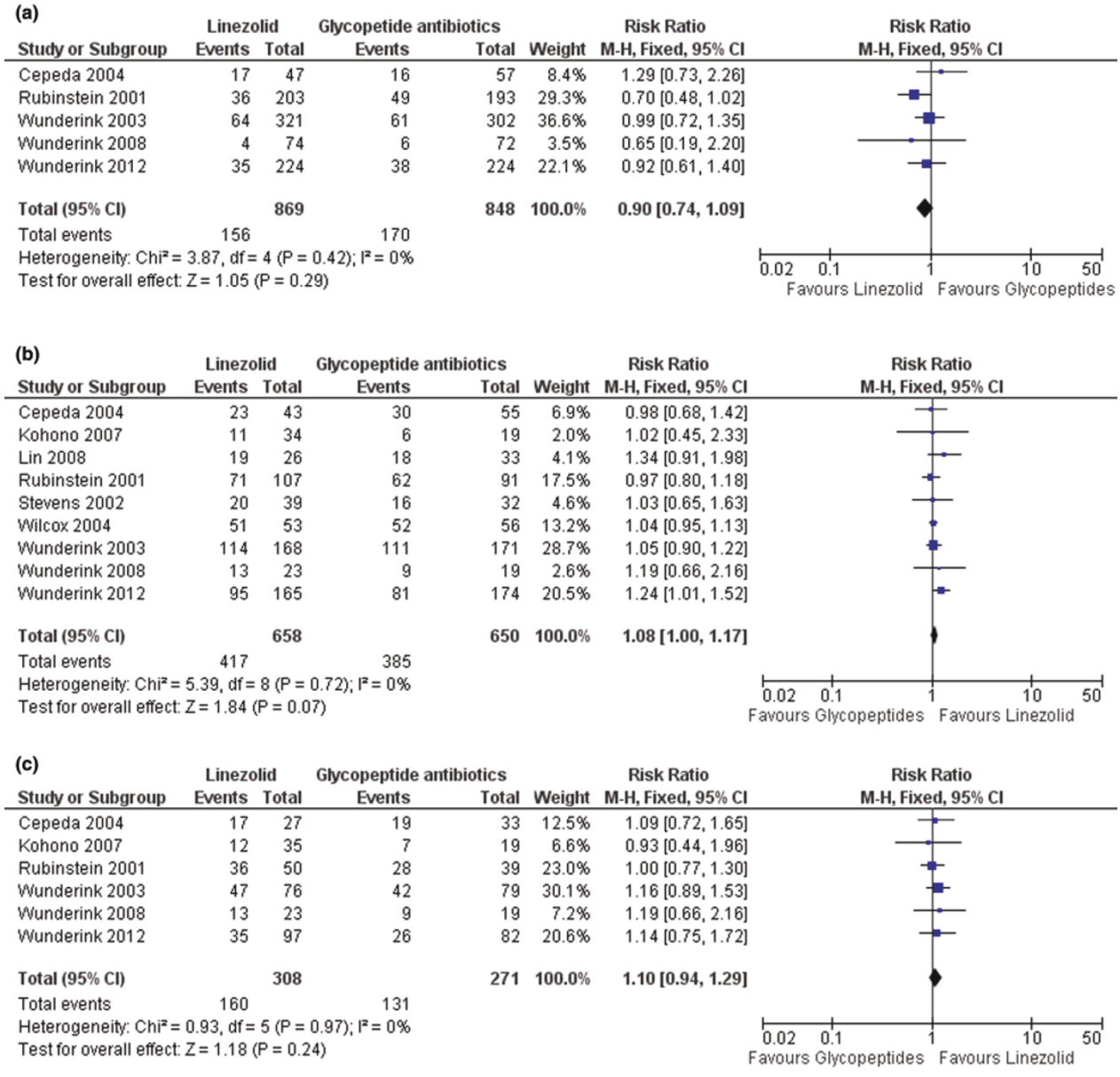

Figure 2. Updated meta-analysis of linezolid versus glycopeptide antibiotics for methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. Updated meta-analysis of **(a)** mortality, **(b)** clinical success and **(c)** microbiological success. CI, confidence interval; M-H, Mantel-Haenszel test.

[42]. Indeed, an antifungal switch to second-line agents was found to be the only risk factor for longer length of stay and increased cost that could be modified, thus highlighting how the choice of an appropriate first-line antifungal agent is crucial for improved outcome.

Andes and colleagues performed a patient-level review of 1,915 patients extracted from seven randomised antifungal treatment trials [43] and found that only removal of central venous catheters and treatment with an echinocandin were associated with improved survival and better clinical outcome than treatment with triazoles or amphotericin-B. Remarkably, the improved outcomes were evident not only for patients infected by *Candida albicans* and non-*albicans* strains but also for infection by *Candida parapsilosis*, which is usually less susceptible to echinocandins (higher MICs) due to the minor quantity of β-D-glucan – the target of echinocandins – within its cell wall. However, echinocandin susceptibility testing with *C. parapsilosis* probably has poor correlation between the MIC results and clinical response. It is still

unclear, indeed, whether there is any clinical relevance to the lower MIC in some isolates of *C. parapsilosis* with treatment response to echinocandins. Moreover, the benefit of such drugs was observed mostly among patients with lower Acute Physiology and Chronic Health Evaluation II scores, whereas outcomes did not differ in the most critically ill patients with invasive candidiasis, who were probably far beyond any successful treatment chance.

Conclusion

Rapid detection of pathogens by molecular methods should be reviewed based on the knowledge of the positive and negative predictive values of various molecular diagnostics and the subsequent antibiotic guidance of the clinicians by, for instance, infectious disease teams. This cooperation remains an important step in an optimal antibiotic stewardship programme. This rapid integration of diagnostics and antibiotic stewardship is essential for achieving better clinical outcomes and streamlining the use of empiric broad-spectrum antibiotics in ICUs. However, several obstacles such as cost issues, 24-hour availability, sample preparation steps and diagnostic accuracy have to be significantly improved in many of the existing PCR assays. Additionally, more clinical trials are required to enhance our knowledge of the clinical relevance of DNAaemia when negative BCs are present.

Despite our obvious need for introduction of new antibiotic drugs in critical care, we are still obliged to assess the true benefit and safety of new drugs before introducing them into clinical practice. This obligation is clearly illustrated by the ongoing controversy surrounding tigecycline [44]. Critical lessons are to be learned from the tigecycline controversy since many of the trials assessing the safety and efficacy of new antibiotics often use a non-inferiority margin of 10 to 15% for the test of clinical response to rule out inferiority of new drugs compared with older drugs [45,46]. This margin results in smaller and often insufficient sample sizes being mainly preferred because of reduced time, costs and efforts when performing a trial. The choice of larger non-inferiority margins may ultimately mask harmful or beneficial effects of new drugs and delay or reject their approval for correct indications [33]. The tigecycline issue clearly contrasts the desire by some to reduce the regulatory approval requirements for new drugs, to mainly focus on animal and *in vitro* minimum inhibitory studies or to use a nonrandomised design to predict drug effectiveness [47].

Beyond the above issues, however, decisions on the choice of antibiotics should depend on multiple factors such as cost, antibiotic resistance, optimal routes of delivery, dosing regimens, pharmacokinetics and local availability of the drug. Finally, rapid diagnostics may ultimately facilitate a more rapid evaluation of new drugs and perhaps better detect subgroups that may benefit most.

Abbreviations

BC, blood culture; BSI, bloodstream infection; CAP, community-acquired pneumonia; CI, confidence interval; CRP, C-reactive protein; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PCR, polymerase chain reaction; PCT, procalcitonin; RCT, randomised controlled trial; VAP, ventilator-associated pneumonia.

Competing interests

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Authors' contributions

All authors read and approved the manuscript, which has not been published nor is under consideration for publication elsewhere.

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