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Consensus document on controversial issues for the treatment of hospital-associated pneumonia

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SUMMARY

Background: Hospital-associated pneumonia (HAP) remains an important cause of morbidity and mortality despite advances in antimicrobial therapy. Many aspects of the treatment of HAP caused by multi-resistant Gram-positive microorganisms have been extensively studied, but controversial issues remain.

Controversial issues: The aim of this GISIG (Gruppo Italiano di Studio sulle Infezioni Gravi) working group – a panel of multidisciplinary experts – was to define recommendations for some controversial issues using an evidence-based and analytical approach. The controversial issues were: (1) Is combination antibiotic therapy or monotherapy more effective in the treatment of HAP? (2) What role do pharmacokinetic/pharmacodynamic antibiotic features have as a guide in the selection of treatment for HAP? (3) Is a de-escalation approach for the management of HAP effective? An analysis of the studies published up until April 2009 is presented and discussed in detail.

Methods: A systematic literature search using PubMed, MEDLINE, and EMBASE databases and the Cochrane Library was performed. A matrix was created to extract evidence from original studies using the CONSORT method to evaluate randomized clinical trials and the Newcastle–Ottawa Quality Assessment Scale for case–control studies, longitudinal cohorts, and retrospective studies. The GRADE method for grading quality of evidence was applied.

1. Introduction

Hospital-associated pneumonia (HAP) is the second most common nosocomial infection (after urinary tract infection) and the most common nosocomial infection acquired in the intensive care unit (ICU).[1–3] HAP associated with mechanical ventilation – ventilator-associated pneumonia (VAP) – has an estimated incidence of 8–28%.[4] VAP is associated with an excess of ICU stay, increased costs,[5,6] and attributable mortality.[6,7]

The etiologic diagnosis of VAP is notoriously difficult, and the results of culture and sensitivity testing are almost always

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available only several days later.[4] On the other hand, the prompt administration of an empirical therapy is considered essential, because inappropriate antimicrobial treatment is an important independent determinant of mortality in patients with VAP, regardless of the introduction of active agents after culture results become available.[8–11] The same results are obtained for *Staphylococcus aureus* respiratory[12] and bloodstream infections.[13]

Based on these observations, the initial therapy should be started immediately after diagnostic specimens are obtained, even though the optimal antimicrobial agents remain unclear, because the microbial and resistance patterns of each local setting are different. Therefore it is evident that recommendations for the initial empiric antimicrobial treatment must be flexible enough for modification according to local peculiarities, and also based on the timing of the episode (early or late VAP), the severity of illness, and previous antibiotic exposure.[14]

If treatment of early VAP (usually due to organisms commonly seen in community-acquired pneumonia, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and methicillin-susceptible *Staphylococcus aureus* (MSSA)) is relatively easy, late VAP or VAP in a patient previously exposed to antibiotics represents a serious problem, because pneumonia is more likely to be caused by multi-resistant organisms such as *Pseudomonas aeruginosa*, *Acinetobacter spp*, and methicillin-resistant *S. aureus* (MRSA).[15,16]

2. Objective

The aim of this work was to define recommendations for some controversial issues on the management of nosocomial pneumonia, using an evidence-based approach.

3. Methods

3.1. Controversial issues

The overall approach to the therapy of HAP is quite complex, and several areas of debate remain. The Italian Study Group on Serious Infections, GISIG, is an Italian nationwide group composed of approximately 50 Italian experts on infectious diseases in the hospital setting and it was committed to study the HAP controversial issues below.

3.2. Combination versus monotherapy

To maximize the probability of adequate antibiotic coverage, combination therapy with two or more broad-spectrum antibiotics is frequently advocated.[14–17] In fact, treatment with multiple antibiotics theoretically increases the likelihood of therapeutic success through an extended spectrum of activity,[18] antimicrobial synergy, especially in the treatment of *P. aeruginosa*,[19] and a decreased potential for promoting resistant microorganisms.[20] On the other hand, combination therapy generally increases the cost and is associated with greater toxicity and the risk of drug–drug interactions; furthermore, there is a risk of the emergence of multi-resistant organisms and superinfections.[15,16,21]

3.3. The role of pharmacokinetic (PK) and pharmacodynamic (PD) antibiotic features as a guide to treatment selection in HAP

To achieve adequate therapy, it is necessary not only to use the correct antibiotic (or antibiotics), but also the optimal dose and the correct route of administration (oral, by aerosol, intravenous, intermittently or continuously administered) to ensure that the antibiotic(s) penetrate(s) the site of infection. When PK/PD parameters have been applied to *in vitro* and animal models, antibiotics have shown a good relationship between concentration and response, when response is quantified as the rate of bacterial eradication.[22–24] Furthermore, most studies correlating PK/PD measures and responses in humans have been conducted to analyze community-acquired pneumonia[25–27] and the common opinion is that the PK/PD properties of specific antibiotics should be considered in selecting an adequate regimen. However, the relevance of these findings to outcomes in the therapy of HAP remains to be defined.

3.4. De-escalation therapy

The criteria for the choice of an initial empiric antimicrobial treatment giving an adequate coverage for the predicted micro-organisms will lead to many patients receiving an initial broad-spectrum therapy, because the risk factors for multidrug-resistant (MDR) pathogens are common. This can potentially lead to antibiotic overuse (i.e., starting antimicrobials for non-infectious diseases or using unnecessary broad-spectrum treatments). Among the proposed strategies to reconcile the need for an appropriate initial empiric coverage with the need to avoid the risks of misuse of broad-spectrum antibiotics, the so-called de-escalation strategies have been the most valued.[28,29] These strategies have in common that, once the results of respiratory tract (and blood culture) examinations become available, the initial broad-spectrum empiric therapy must be focused or narrowed (de-escalated) on the basis of the identification of specific pathogens and their antimicrobial *in vitro* susceptibility. This 'de-escalation' approach is supported by many authors, but criteria for its application and the real impact on clinical outcomes deserve further consideration.[30]

3.5. Literature search and study selection

3.5.1. Question 1: combination versus monotherapy

The study selection was arranged in two phases. The first phase aimed to collect all recent reviews and guidelines based on systematic revisions and the second phase intended to select recent randomized controlled trials (RCTs) not included in previous systematic revisions.

For the first step we searched PubMed (up to April 2009) and citations of the included reviews with the terms: (('pneumonia' AND 'cross infection') OR 'ventilator associated pneumonia' OR 'nosocomial pneumonia') AND 'guidelines' . We included studies using these limits: published in the last 10 years, in humans, meta-analysis, practice guideline, review, government publication, guideline, English, French, Italian, Spanish. The same terms were used for a further search in Medline, EMBASE, and the Cochrane Library.

The second phase of the research was performed using PubMed (up to April 2009) and citations of included trials with the terms: (('pneumonia' AND 'cross infection') OR 'ventilator associated pneumonia' OR 'nosocomial pneumonia') AND 'anti bacterial agents' AND 'randomized controlled trial' . We included studies using these limits: published in the last 2 years, in humans, clinical trial, randomized controlled trial, clinical trial phase III, clinical trial phase IV, comparative study, English, French, Italian, Spanish. The same terms were used for a further search in Medline, EMBASE, and the Cochrane Library.

In this double-step selection we detected a total of 201 studies (167 from the first and 34 from the second search). We included all studies fulfilling the following PICOD criteria:

- P Hospital-acquired pneumonia, including ventilator-associated pneumonia
- I Combination antibiotic therapy
- C Antibiotic monotherapy

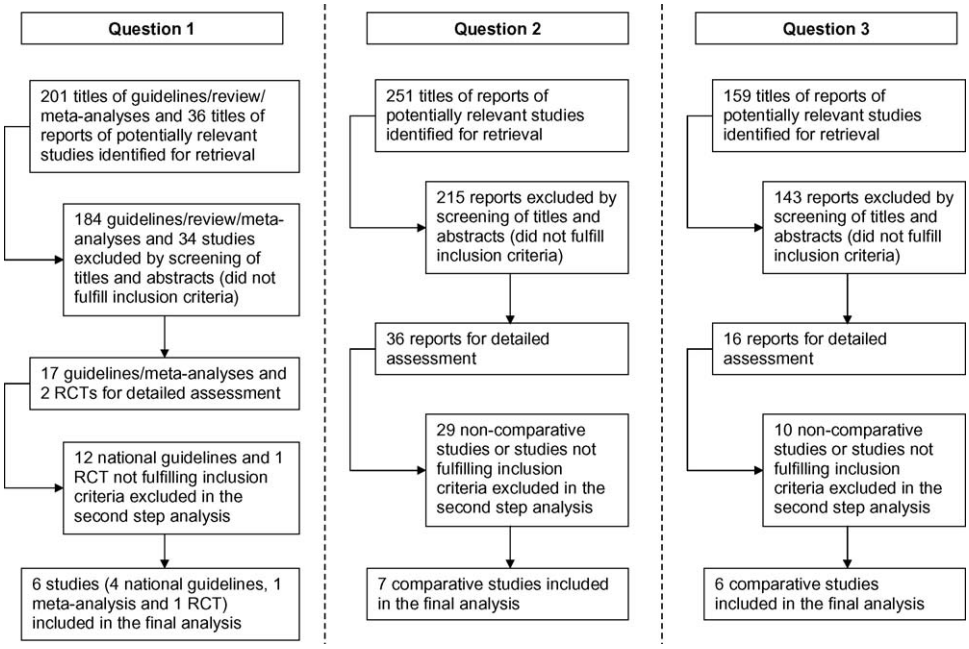

Figure 1. Flow-chart of studies included in the final analysis.

- O Clinical and/or microbiological response, mortality, super-infections and adverse events
- D Randomized controlled trials

In recent years, the question about the superiority of antibiotic combination therapy compared with monotherapy has been the subject of several reviews, and many scientific societies have tried to deal with this difficult subject. For our review of the literature we initially screened 201 meta-analyses, practice guidelines, reviews, government publications, and guidelines.

After the exclusion of all the reviews or guidelines that had not indicated the methodology criteria for the analysis of the literature or that had not dealt with the query 'combination or monotherapy?', only four national guidelines[14,31–33] and one systematic review of good quality remained.[34] Out of the two available RCTs,[35,36] only one was considered of high quality and was included (Figure 1).[36]

3.5.2. Question 2: the role of pharmacokinetic and pharmacodynamic antibiotic features as a guide to treatment selection in HAP

We searched PubMed, Medline, EMBASE, and the Cochrane Library (up to April 2009) and citations of included studies with the terms: (('pneumonia' AND 'cross infection') OR 'ventilator associated pneumonia' OR 'nosocomial pneumonia') AND 'Gram-positive bacteria' AND 'anti bacterial agents' AND ('pharmacokinetics' OR 'pharmacodynamics'). We included studies in English, French, Italian, and Spanish regardless of date of publication. In this search we detected a total of 251 studies. We included all studies fulfilling the following PICOD criteria:

- P Hospital-acquired pneumonia due to Gram-positive pathogens, including VAP and health care-associated pneumonia (HCAP)
- I Higher PK/PD values
- C Lower PK/PD values
- O Clinical and/or microbiological response, mortality, emergence of antibiotic resistance
- D Comparative study in humans

After screening of the 251 articles, we excluded 244 studies because they were not comparative studies (reviews, guidelines, expert opinions, consensus conferences, case series or case reports), the experimental design excluded human populations (*in vitro* or animal models, mathematical models), the population showed no infectious pathology (human volunteers, chronic obstructive pulmonary disease (COPD), cystic fibrosis, etc.) or infectious diseases other than pneumonia (otitis, endocarditis, bacteremia, etc.), HAP was due to Gram-negative organisms or fungi only, or there was an absence of any correlation to clinical or microbiological outcome. Finally, observational studies that did not provide sufficient data to calculate an odds ratio for clinical outcome were not considered (Figure 1).

3.5.3. Question 3: de-escalation therapy

We searched PubMed, Medline, EMBASE, and the Cochrane Library (up to April 2009) and citations of included studies with the terms: (('pneumonia' AND 'cross infection') OR 'ventilator associated pneumonia' OR 'nosocomial pneumonia') AND 'anti bacterial agents' AND ('de-escalation' OR 'discontinuation' OR 'treatment guideline' OR 'antibiotic guideline'). We included studies in English, French, Italian, and Spanish, regardless of date of publication. In this search we detected a total of 159 studies. We included all studies fulfilling the following PICOD criteria:

- P HAP due to Gram-positive pathogens, including VAP and HCAP
- I A de-escalation strategy
- C Standard of care
- O Clinical and/or microbiological response, mortality, emergence of antibiotic resistance, hospital or ICU length of stay, costs
- D RCT or other comparative study in humans

We screened 159 studies for inclusion in this review. The principal reasons for exclusion of the study from the analysis were: because they did not adequately compare de-escalation with a different strategy, did not use clinical outcome measures, included only patients with Gram-negative infections, or analyzed primarily the role of empiric therapy guided by colonization data obtained from endotracheal aspirates. Also studies disguised as reviews (guidelines, expert opinions and consensus conferences) were excluded.

A total of 10 papers concerning a de-escalation strategy were considered. However, the final analysis does not include four

observational studies that retrospectively compared patients on de-escalating antibiotic treatment versus patients not de-escalating.[37–40] In spite of their potential interest, the retrospective nature of these investigations introduced a high risk of bias, because of the decision not to de-escalate antibiotics. Therefore, the final analysis was performed on six trials (Figure 1).

3.6. Classification and evaluation of the selected evidence

Statement documents (guidelines and/or consensus statement) and review documents (systematic review of the literature and meta-analyses) were chosen on the basis of the presence of a methods section with inclusion criteria, methodology used to identify the studies, and quality evaluation of the included studies.

A matrix was made to extract evidence from each original study using the CONSORT method for RCTs and the Newcastle–Ottawa Quality Assessment Scale for case-control studies, longitudinal cohorts, and retrospective studies with comparative evaluations. To assign the strength level for each recommendation, a methodology adapted from the GRADE Working Group was used. The details of the applied methodology are published in this supplement.[41]

4. Results

4.1. Question 1: combination versus monotherapy

The guidelines elaborated by the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) in 2005[14] analyzed data from a few trials.[42,43] The conclusion was that no data have documented the superiority of antibiotic combination therapy compared with monotherapy, except to enhance the likelihood of initially appropriate empiric therapy. The former approach should be used if patients are likely to be infected with MDR pathogens.

In the guidelines from Brazil and Argentina,[31] on the basis of an analysis of a few studies,[44–46] the authors are convinced that monotherapy in the treatment of HAP without MDR strains reduces costs and unnecessary exposure to antibiotics .

The more recent guidelines of the British Society for Antimicrobial Chemotherapy (BSAC)[32] revised the results of 16 RCTs enrolling patients with HAP (but not exclusively) and comparing patients receiving monotherapy with combination therapy with an aminoglycoside.[42,43,45,47–58]

From the above studies, there is no evidence that clinical or bacteriological response rates can be improved with combination therapy.

Finally, the VAP Guidelines Committee and the Critical Care Trials Group from Canada[33] extrapolated data from five level 2 trials,[35,47–49,59] concluding that there is no advantage to antibiotic combination therapy, because these trials did not demonstrate any differences in mortality or clinical response rates. In addition, the benefit of a reduction in antibiotic use and costs favors monotherapy. However, these authors argued that knowledge of the nature and susceptibility of the environmental pathogens remains the cornerstone to correctly prescribe antibiotic therapy.

All guidelines agree, however, that in settings with a high probability of MDR organisms, combination therapy is recommended even if there is no clear evidence from the studies, which suffer from lack of power and low numbers of infections caused by MDR bacteria.

A complete evaluation of this topic is included in the systematic review of Aarts et al. on the management of HAP.[34] On the basis of stringent criteria, the authors selected 11 trials comparing monotherapy with combination therapy,[42,43,45,47–50,59–63] including a total of 1805 patients (85.1% ventilated). Monotherapy consisted of a carbapenem (n = 5), ceftazidime (n = 3), cefepime, ciprofloxacin, or moxalactam (n = 1). Combination therapy consisted of ciprofloxacin

Table 1
Question 2: characteristics of the studies

Study	Design	Centers	Inclusion criteria	Nosocomial only	Principal exclusion criteria	Antibiotic used	*S. aureus* (%)	MRSA (%)	GRADE score
Moise, 2000[67]	Retrospective cohort study	1	*S. aureus* LRTI	No	Extra-pulmonary	Vancomycin	100%	50%	1
Wysocki, 2001[69]	Randomized controlled trial	10	MRS severe infections	Yes	Renal failure; neutropenia; MOF	Vancomycin	100%[a]	80%[a]	4
Moise-Broder, 2004[68]	Retrospective cohort study	1	*S. aureus* LRTI	No	–	Various (vancomycin 58%)	100%	30%	4
Drusano, 2004[66]	Retrospective cohort study	67	HAP not severe	Yes	APACHE II >35; renal failure	Levofloxacin	36%	NE	3
Hidayat, 2006[70]	Retrospective cohort study	1	MRSA infection	Yes	–	Vancomycin	100%	100%	2
Jeffres, 2006[64]	Retrospective cohort study	1	MRSA HCAP	Yes	Polymicrobial infection	Vancomycin	100%	100%	2
Jeffres, 2007[65]	Retrospective cohort study	1	MRSA HCAP	Yes	Polymicrobial infection, renal failure	Vancomycin	100%	100%	2

LRTI, lower respiratory tract infection; MRS, methicillin-resistant staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; MOF, multiorgan failure; HAP, hospital-acquired pneumonia; HCAP, health care-associated pneumonia; APACHE, acute physiology and chronic health evaluation score; NE, not evaluated. [a] Including *Staphylococcus* spp., not only *S. aureus*.

combined with meropenem ($n = 1$), cefepime combined with levofloxacin or amikacin ($n = 1$), or an aminoglycoside combined with ceftazidime ($n = 5$) or other anti-pseudomonal β-lactams ($n = 4$). There was no mortality difference (in the eight studies evaluating this outcome) for patients receiving monotherapy in comparison to combination therapy (relative risk (RR) 0.94, 0.76–1.16). Similarly there was no significant difference in treatment failure (RR 0.88, 0.72–1.07), rates of superinfection (RR 0.77, 0.48–1.22), or serious adverse events (RR 0.84, 0.48–1.49). The only evidence of superior efficacy comparing specific antibiotic regimens was seen in six trials pooled in three comparisons showing meropenem to be superior to a combination of ceftazidime and an aminoglycoside in terms of clinical response (RR 0.70, 0.53–0.93).

Aarts and colleagues[34] concluded that there was no evidence that combination therapy is superior to monotherapy in reducing rates of treatment failure, superinfection, or adverse events. Meropenem was associated with a decreased treatment failure rate when compared with ceftazidime and aminoglycoside combination therapy, but without differences in mortality.

However, the authors specified that the percentage of episodes of VAP caused by MDR or difficult-to-treat organisms was low in the trials they reviewed, and that the initial selection of antimicrobial(s) must be guided by consideration of local microbial ecology.

After the meta-analysis of Aarts,[34] only one RCT on this topic deserving consideration has been published. In the USA and Canada, Heyland et al. performed a multicenter study comparing a strategy of combination therapy (meropenem plus ciprofloxacin) with a strategy of monotherapy (meropenem) for the treatment of suspected late-onset VAP.[35] Patients colonized or infected with *P. aeruginosa* or MRSA were not included in the 740 mechanically ventilated patients studied. Consequently, the overall prevalence of *P. aeruginosa*, MRSA, and other MDR organisms was negligible (MRSA 1.6% and MDR Gram-negative organisms 7.6%).

The relative risk of 28-day mortality in the combination group vs. monotherapy group was 1.05 (0.78–1.42, $p = 0.74$) after stratification for APACHE II score and diagnostic technique. Duration of ICU and hospital stay, clinical and microbiological response, emergence of antibiotic-resistant bacteria, isolation of *Clostridium difficile* in stool, and fungal colonization were also similar in the two groups.

The authors stated that monotherapy is associated with similar outcomes compared with combination therapy, but limited their conclusion to patients with suspected late VAP at low risk for difficult-to-treat Gram-negative bacteria or MRSA.

4.2. Question 2: the role of pharmacokinetic and pharmacodynamic antibiotic features as a guide to treatment selection in HAP

We identified seven studies for analytical evaluation (Tables 1 and 2). The characteristics of these studies were quite different and only three out of the seven studies included HAP only. Two of these three involved the same group and included only HCAP caused by MRSA.[64,65] In the third one, including non-severe HAP, *S. aureus* accounted for more than one third of the episodes.[66]

Jeffres et al., in a single-center observational cohort study, used targeted trough concentrations of 15–20 mg/l to retrospectively evaluate 102 patients with health care-associated MRSA pneumonia.[64] The study failed to demonstrate any relationship between vancomycin PK indices and mortality. The multivariate analysis identified vasopressor administration and COPDs as the only independent determinants of hospital mortality, even because the trough levels and area under the curve (AUC) were very similar in survivors and non-survivors (Table 2).

In a second study, Jeffres et al. included 94 patients with HCAP in order to evaluate the relationship between aggressive vancomycin dosing and nephrotoxicity.[65] Patients who developed nephrotoxicity were more likely to have higher steady-state mean trough serum vancomycin concentrations (20.8 mg/l vs. 14.3 mg/l, $p < 0.001$). Longer duration (≥14 days) of vancomycin therapy (45.0% vs. 20.4%, $p = 0.011$) was also correlated with nephrotoxicity.

Drusano et al. retrospectively examined 47 patients with non-severe HAP who were treated with levofloxacin, demonstrating that a total drug AUC_{24}/minimum inhibitory concentration (MIC) value ≥87 was correlated with the eradication of Gram-negative bacilli ($p < 0.011$).[6] However, logistic regression analysis of clinical outcomes revealed no link between AUC_{24}/MIC ratio and this parameter. In this study, a second antibiotic was added for patients with MRSA or *P. aeruginosa* infection (vancomycin for MRSA and ceftazidime or piperacillin/tazobactam for *P. aeruginosa*). However, the 'other active drugs' covariate was not significant in univariate analysis.

The other four studies did not completely meet the inclusion criteria of the research, but furnish useful supplementary information. In particular, two studies by the same group retrospectively analyzed episodes of *S. aureus* lower respiratory tract infection (LRTI) (with variable rates of MRSA, from 30% to 50%), not exclusively of nosocomial origin[67,68] and two studies analyzed a population of methicillin-resistant staphylococcal infections, not exclusively affecting the respiratory tract.[69,70]

Moise et al. studied a group of 70 patients (53 clinically evaluable and 62 microbiologically evaluable) with LRTIs caused by *S. aureus* using the AUC_{24}/MIC of vancomycin to predict clinical and microbiological outcomes.[67] The AUC_{24}/MIC of clinical non-responders was 380.5 ± 218.2 mg/l (median 306 mg/l) vs. 628.3 ± 368.1 mg/l (median 491 mg/l) for patients with successful clinical outcomes ($p = 0.001$). Moreover, microbiological success was reached in 91% of patients with AUC_{24}/MIC >866, whereas

Table 2
Question 2: results of the studies

Study	*n*	PK/PD parameter	Clinical response	Microbiological response	Nephrotoxicity
Moise, 2000[67]	70	AUIC	0.001	Yes[a]	NE
Wysocki, 2001[69]	119[b]	Trough, AUC	<0.05[c]	NE	NE
Moise-Broder, 2004[68]	90	AUIC	0.004	0.04	NE
Drusano, 2004[66]	47	AUIC	NS	<0.001[c]	NE
Hidayat, 2006[70]	95	Trough	NS	NA	0.01
Jeffres, 2006[64]	102	Trough, AUC	NS	NE	NE
Jeffres, 2007[65]	94	Trough	NE	NE	0.01

PK/PD, pharmacokinetic/pharmacodynamic; AUIC, area under the curve on minimal inhibitory concentration ratio; ID, immunodepression; HCAP, health care-associated pneumonia; LRTI, lower respiratory tract infection; MRS, methicillin-resistant staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable; NE, not evaluated; NS, not significant.

[a] High correlation with microbiological success but no *p*-value calculated.

[b] Including *Staphylococcus spp*, not only *S. aureus*.

[c] *p*-value not significant in multivariate analysis.

Table 3
Question 3: characteristics of the studies

Study	Design	Inclusion criteria	Exclusion criteria[a]	Patients with no bacterial isolation	Gram-pos (MRSA) %	Type of de-escalation	Guideline	Comparator	Antibiotic used	Grade score[b]
Prospective randomized controlled trials comparing protocols of early discontinuation vs. common practice										
Singh, 2000[71]	RCT	Presumed VAP	HIV, neutropenia	Included	29%[c] (NA)	Discontinuation	local (stop if CPIS < 6 after 3 days)	Physician judgment	Ciprofloxacin vs. free choice	>4
Micek, 2004[73]	RCT	Presumed VAP	None	Considered adequately treated	31.7%[c] (19.7%)	Discontinuation	Local	Physician judgment	As protocol	>4
Before and after studies comparing guidelines-oriented de-escalation strategy vs. common practice										
Ibrahim, 2001[74]	Prospective before–after	VAP	Neutropenia, bacteremia, lung transplant	Considered adequately treated	40.2% (21.5%)	De-escalation	Local (pre-ATS) + short therapy (7 days)	Physician judgment	Imipenem. ciprofloxacin, vancomycin	3
Soo Hoo, 2005[75]	Retrospective observational cohort study	Severe HAP	HAP mild–moderate	Included	48.7% (39.3%)	De-escalation	local	Physician judgment	As protocol	3
Dellit, 2008[76]	Retrospective before–after	HCAP	None	Included (separately analyzed)	43.0% (14.1%)	De-escalation	ATS + short therapy (7 days)	Physician judgment	As protocol	2
Lancaster, 2008[77]	Prospective before–after	Proven or suspected VAP	HCAP; HIV; transplant; neutropenia	Included	43.7% (10%)	De-escalation	ATS + short therapy (8 days)	Common practice	As protocol	4

MRSA, methicillin-resistant *Staphylococcus aureus*; RCT, randomized controlled trial; VAP, ventilator-associated pneumonia; HIV, human immunodeficiency virus; NA, not available; CPIS, clinical pulmonary infection score; ATS, American Thoracic Society; HAP, hospital-acquired pneumonia; HCAP, health care-associated pneumonia.

[a] All studies (apart from Dellit and Soo Hoo) excluded patients aged <18 years.

[b] The grade score was calculated using clinical response or mortality as reference outcome.

[c] Data on staphylococci only.

patients with AUC_{24}/MIC <866 had only a 39% success rate (no statistical analysis is presented). Authors concluded that AUC_{24}/MIC predicts clinical and microbiological outcomes of vancomycin therapy in patients with *S. aureus* LRTI. However, a multivariate analysis of other risk factors potentially correlated to the outcomes was not available.

In another study, the same group aimed to determine whether the time that vancomycin serum concentrations exceed the MIC (%time > MIC) is as good a determinant of response as its AUC_{24}/MIC value and to examine the time to bacterial eradication for vancomycin in relation to achieved AUC_{24}/MIC values.[68] The stepwise logistic regression identified five statistically significant factors associated with improved clinical outcome, among them AUC_{24}/MIC >350 (OR 7.19, $p = 0.004$) was the more important. Moreover, the time to bacterial eradication was significantly lower in patients with an AUC_{24}/MIC > 400 (median 10 days vs. an excess of 30 days, $p = 0.04$). Finally, all the patients in the study (both successes and failures) had %time > MIC = 100%, establishing that this target is not predictive of outcome. The authors concluded that the AUC_{24}/MIC ratio predicts time-related clinical and bacteriological outcomes for patients with LRTI caused by MRSA and appears to be the major pharmacodynamic index correlating with infection response.

In a multicenter, prospective, randomized study, Wysocki et al. evaluated 119 patients with severe hospital-acquired staphylococcal infections (pneumonia, 45%), of which 80% were methicillin-resistant.[69] The aim of the study was to determine which modality of vancomycin infusion is more efficient, safer, easier to adjust, and more cost-effective. Two schemes were compared: intermittent vancomycin infusion (IVI) and continuous vancomycin infusion (CVI). Trough concentrations and AUC_{24} were higher for patients who failed in comparison with those with treatment success ($p < 0.05$ in univariate analysis). However, a multivariate analysis found that only the severity of the underlying disease at admission ($p < 0.05$) and the day-10 serum creatinine concentrations ($p < 0.02$) were associated with treatment failure. Reduced costs (calculated for 10 days and defined as the cost of vancomycin infused plus the cost of monitoring vancomycin concentrations in serum) were obtained with CVI. The conclusion of the investigators was that no difference in patient outcome was observed between those receiving intermittent and those receiving continuous infusion of vancomycin.

Hidayat et al. investigated 95 elderly patients with health care-associated infections due to MRSA.[70] Most isolates came from the respiratory tract (52%), and co-infection with *P. aeruginosa* and/or *Enterobacteriaceae* was present in 28% of patients with pneumonia. Vancomycin MIC values of 1.5 or 2 mg/l were found in 54% of the patients. The authors evaluated the efficacy and risk of nephrotoxicity after the use of high-dose vancomycin intended to achieve unbound trough serum vancomycin concentrations of at least four times the MIC. Patients infected with MIC >1 mg/l strains had a poorer response (62% vs. 85%) and a significantly higher infection-related mortality (24% vs. 10%), despite achieving target trough serum vancomycin concentrations of 15–20 mg/l. In a multivariate analysis, the MIC of the infected strains and APACHE II score ($p = 0.03$ and 0.009, respectively) were independent predictors of poor treatment response when controlled for target trough attainment. Concomitant nephrotoxic agents ($p < 0.001$), high vancomycin trough level ($p = 0.03$), and duration of vancomycin therapy ($p = 0.004$) significantly predicted nephrotoxicity. By controlling for other factors (including vancomycin trough levels and duration of therapy) in a multivariate analysis, concomitant nephrotoxic agents remained the most significant predictor of nephrotoxicity ($p = 0.003$).

Table 4
Question 3: results of the studies

Study	*n*	Mortality	Appropriate antibiotic	Duration of antibiotic	LOS hospital	LOS ICU	Clinical response	Colonization	Induction of resistance	Super infection	Cost
Prospective randomized controlled trials comparing protocols of early discontinuation vs. common practice											
Singh, 2000[71]	81	NS	NE	0.0001	NE	0.04	NS	NE	0.017	0.0001	0.003
Micek, 2004[73]	290	NS	NE	0.001[a]	NS	NS	NE	NE	NE	NS	NE
Before and after studies comparing guidelines-oriented de-escalation strategy vs. common practice											
Ibrahim, 2001[74]	102	NS	<0.001	<0.001	NS	NS	NE	NS[b]	NE	0.03	NE
Soo Hoo, 2005[75]	117	0.03[c]	<0.01	NE	NS	NS	NE	NS	NS	NE	NE
Dellit, 2008[76]	819	NS	0.001[d]	0.001[e]	NE	NE	NE	NE	NE	NE	NE
Lancaster, 2008[77]	100	NS	0.005[f]	0.001	NS	NS	NE	NE	NE	NE	NE

LOS, length of stay; ICU, intensive care unit; NE, not evaluated; NS, not significant.
[a] Statistical significance was <0.001 in the subgroup of Gram-positive pneumonia.
[b] Only colonization by vancomycin-resistant enterococci was considered.
[c] Mortality at 30 days was not significant.
[d] Initial empiric antibiotic therapy was not significant, but definitive antibiotic treatment was significant.
[e] Statistical significance was 0.009 in the methicillin-susceptible *Staphylococcus aureus* subgroup and 0.042 in methicillin-resistant *Staphylococcus aureus* subgroup.
[f] Different analyses to evaluate appropriateness.

4.3. Question 3: de-escalation therapy

A first attempt to evaluate a strategy of de-escalation in patients with VAP was proposed by Singh et al.,[71] and adopted an approach using the first five variables of the clinical pulmonary infection score (CPIS)[72] – temperature, blood leukocyte count, tracheal secretions, oxygenation, and character of pulmonary infiltrate – as criteria to identify patients for whom a shorter course of antibiotic therapy would suffice. In their RCT, these investigators were able to demonstrate that pneumonia can be reasonably excluded and empirical antibiotic therapy stopped when the CPIS falls below 6 at baseline and again at 3 days. Notwithstanding the limited number of patients included in the study ($n = 81$), overall, a substantial reduction in antibiotic use ($p = 0.0001$) and costs ($p = 0.003$), and in length of stay ($p = 0.0001$) was observed. Moreover, antimicrobial resistance, or superinfections, or both, developed in 15% of the patients in the discontinuation group versus 35% of the patients in the standard therapy group ($p = 0.017$).

More recently, Micek et al. evaluated an easy antibiotic discontinuation policy for VAP based on the presence of one of the following conditions: (1) non-infectious etiology for the infiltrates; and (2) signs and symptoms suggesting active infection resolution.[73] The antibiotic treatment at baseline was a combination of linezolid or vancomycin plus cefepime plus ciprofloxacin or gentamicin. The authors also decided to include patients without isolation of pathogenic microorganisms in their respiratory cultures, and considered them adequately treated (20% and 25% in the discontinuation and conventional groups, respectively). The data analysis for the 290 patients completing this RCT demonstrated a shorter duration of antibiotic treatment in the discontinuation group ($p = 0.001$). Moreover, the occurrence of a secondary episode of VAP and hospital and ICU length of stay were no different between the two groups.

These strategies of early discontinuation are similar to the concept of de-escalation, but are based on an early re-discussion of the diagnosis (yes/no) of pneumonia rather than on the pathogen and its susceptibility pattern.

The validity of a multi-step protocol of de-escalation has been verified in the prototype study of Ibrahim et al.,[74] which confirmed the three 'before and after' investigations performed in recent years by Soo Hoo et al., Dellit et al., and Lancaster et al.[75–77] The model guide for the de-escalation of antibiotics did not significantly diverge from the ATS guidelines in all the studies, which differed principally in the patient inclusion criteria (see Table 3) and in the criteria for dealing with patients without a bacterial isolation. All the studies evaluated mortality and appropriateness of antibiotic treatment, but in the definition of this latter item all the studies considered only the activity *in vitro* against the identified bacterial species associated with HAP.

As summarized in Tables 3 and 4, all these publications have demonstrated the positive impact of institution-specific guidelines for the management of HAP patients with different characteristics: HCAP,[76] severe HAP,[75] and VAP.[74,77] The benefits include improvements in the appropriateness of empirical therapy,[74,75,77] reduction in duration of antibiotics,[74,76,77] development of secondary episodes of VAP by MDR bacteria, colonization by vancomycin-resistant enterococci (VRE),[74] and mortality at 14 days.[75] In none of the studies was protocol-guided de-escalation inferior in whatever parameter in comparison with the clinical judgment of the physician as observed in the 'before period'. All these investigations are inevitably affected by the limits of this type of study: although the authors tend to demonstrate the comparability of the two periods under examination, multiple factors influencing outcomes are varied and determine the results of the studies. Notably, in the protocols of three out of the four studies, a time limit of 7–8 days for the duration of the antibiotic treatment was included, after which the therapy had to be interrupted (except for patients with Gram-negative pathogens, such as *P. aeruginosa* and *Acinetobacter baumannii*, in which case a longer duration of 15 days was recommended).[74,76,77]

5. From the evidence to the recommendations

5.1. Question 1: combination versus monotherapy

5.1.1. Discussion

The analysis of several RCTs comparing monotherapy with combination treatment in the antibiotic treatment of HAP, does not substantiate any advantage for combination therapy[34] (GRADE score 1). There are several limitations in these trials. They were often performed in heterogeneous populations and this may have diluted the impact of particular antibiotic regimens in patients with a specific diagnosis of VAP. They were generally small, without the power to detect differences in outcomes between the treatment groups. They did not evaluate the timing of administration, which could be a factor more important than the type of antibiotic(s) administered. However, the major limitation is the very low percentage of episodes of VAP caused by MDR bacteria. Therefore, the proposal of an antibiotic monotherapy has to be reserved for settings in which MRSA or other difficult-to-treat pathogens are not frequently found.

Meropenem was associated with a decreased treatment failure rate when compared with ceftazidime and aminoglycoside (tobramycin or amikacin) combination therapy[43,47] (GRADE score 2 for both). This effect, however, did not translate into a difference in mortality. On the other hand, double β-lactam or β-lactam–fluoroquinolone combinations have not been studied adequately.

Because of their design, the data available from pertinent RCTs do not allow any conclusions to be drawn on the potential advantages of also prescribing a drug that is active against MRSA or other MDR Gram-positive agents in the initial empiric treatment of VAP, which is a frequent practice where MRSA is endemic. In published studies, initially untreated MRSA often appears to be the cause of treatment failure,[78,79] but no specific trials testing initial coverage also of MRSA against a comparator arm without this coverage, are available. Several studies have investigated the efficacy of linezolid, vancomycin, teicoplanin, and ceftobiprole in the treatment of HAP[80–82] (GRADE score 4, 4, 0, respectively) and severe pneumonia[83,84] (GRADE score 1 for both), but have always compared two potentially active treatments.

Therefore, additional studies are needed to provide advice to clinicians on the optimal agents and dosages for treating HAP in patients with risk factors for MRSA. Up-to-date guidelines could be used to correctly identify these patients[14] (quality level 2).

Recommendations

The initial selection of the antimicrobial regimen for HAP must be guided by consideration of the local microbial ecology. In populations of patients at low risk of MDR (including MRSA) or difficult to-treat pathogens, therapy with a single antibiotic may be adequate (A).

We advocate that in patients with HAP at risk for MRSA, initial empiric combination therapy including linezolid or a glycopeptide should be prescribed and rationalized based on culture results (see also de-escalation strategy) (D).

5.2. Question 2: the role of pharmacokinetic and pharmacodynamic antibiotic features as a guide to treatment selection in HAP

5.2.1. Discussion

The investigations described herein are often limited by a small sample size, retrospective design, and questionable methodology. None of the studies evaluated mortality as an outcome and only the study of Wysocki included an analysis of costs[69] (GRADE score 4). Based on these study results, there are no conclusive data suggesting a strong correlation between PK (trough concentration and AUC) and clinical outcome in HAP[64,65,69,70] (GRADE score 2, 2, 4, 2, respectively).

Regarding PD parameters, the AUC_{24}/MIC has been correlated with microbiological outcome for levofloxacin[66] (GRADE score 3) and with both microbiological and clinical outcome for vancomycin.[67,68] (GRADE score 1 and 4, respectively). An AUC_{24}/MIC ratio of $\geq$350 has been advocated as a target for the achievement of clinical efficacy with vancomycin[68] (GRADE score 4), and of $\geq$87 for levofloxacin[66] (GRADE score 3). According to current understanding, AUC_{24}/MIC is likely the PK/PD surrogate marker that better predicts clinical efficacy, although the main data on vancomycin were obtained in a population with *S. aureus* LRTI, not exclusively nosocomial. Even though data regarding Gram-positive infections are lacking, literature data on Gram-negative pneumonia shows favorable results in the correlation between AUC_{24}/MIC and clinical as well as microbiological outcome[85] (GRADE score 1) and in the adjustments of dosing based on PK/PD parameters[86] (GRADE score 1).

The studies analyzing the relationship between vancomycin levels and nephrotoxicity in patients with MRSA infections showed that higher trough serum vancomycin levels may increase the potential for toxicity[65,70] (GRADE score 2 for both). However, these limited data are characterized by the presence of confounding nephrotoxic agents[70] (GRADE score 2) and by the difficulties in examining the timing of the relationship between high vancomycin levels and nephrotoxicity (i.e., which one precedes the other). However, Darko et al., investigating patients with different infections, found therapeutic drug monitoring to be cost-effective among ICU patients and those receiving other nephrotoxic drugs[87](GRADE score 1). Therefore, additional clinical experience is required to determine the extent of this potential in the management of patients with HAP.

Concentrations in epithelial lining fluid (ELF) greater than or equal to those in the serum achieved by some antibiotics (fluoroquinolones, macrolides, and linezolid) may contribute to enhanced efficacy[88–91](GRADE score 1 for each). However, vancomycin has been shown to have lower penetration into the ELF and respiratory secretions[92,93] (GRADE score 1 for both). It is not clear whether these differences relate to clinical outcomes in patients with HAP, because studies analyzing ELF levels of antibiotics and clinical outcomes in HAP are not available.

Recommendations

We encourage the use of PK/PD parameters such as AUC_{24}/MIC ratio, at least for critically ill patients with HAP, for the prevention of both failure and resistance (B). Because it can be difficult in the clinical setting to obtain multiple serum vancomycin concentrations to determine the AUC and subsequently the AUC_{24}/MIC, trough serum vancomycin concentration monitoring can be recommended when MIC is available, in attempting to increase trough serum vancomycin concentrations to 15–20 mg/l to obtain a desirable AUC/MIC of $\geq$400 (C). Because the target attainment of an AUC_{24}/MIC of $\geq$400 for vancomycin is not likely in patients with *S. aureus* infections who have a MIC of $>$1 mg/l, treatment with alternative agents should be considered (C).

Monitoring of trough serum vancomycin concentrations to reduce nephrotoxicity is recommended for patients receiving aggressive dosing ($>$30 mg/kg) and/or receiving concurrent nephrotoxic drugs and/or with unstable renal function and/or receiving prolonged courses of therapy (over 5 days) (B).

5.3. Question 3: de-escalation therapy

5.3.1. Discussion

The use of protocols for the de-escalation of antibiotics in the management of HAP based on international guidelines and local microbiological data have demonstrated positive results. The major impact identified in the 'before and after' investigations was in terms of appropriateness of empirical therapy[74–77] (GRADE score 3, 3, 2, 4, respectively) and reduction in duration of antibiotics[74,76,77] (GRADE score 3, 2, 4, respectively). Furthermore, retrospective observational studies also suggest that de-escalation therapy may be safe, because under no circumstances was prolonged broad-spectrum empirical antibiotic therapy superior to de-escalation regimens[37–40,94] (GRADE score 1 for each). However, the comparisons remain doubtful in that one well-standardized strategy (de-escalation protocol) is tested against a clinical strategy that could reflect an incorrect clinical practice. Therefore the true use of targeted therapy in all patients with VAP should be confirmed through the conduct of RCTs comparing early empiric therapy to a strategy of delayed therapy based on culture results.

There are limited data concerning the optimal duration of therapy for patients with HAP. A recent RCT showed no statistically significant differences in mortality and recurrences of pneumonia, comparing 8 versus 15 days of antibiotic treatment[95] (GRADE score 3). The only exception was the higher rates of recurrence among patients infected with non-lactose-fermenting bacteria (*P. aeruginosa* and *Acinetobacter*). Consequently, most of the de-escalation protocols recommend a 7- or 8-day course of adequate antibiotic

therapy. A duration of 15 days has been suggested for patients infected with *P. aeruginosa* or *A. baumannii* or if there is a lack of clinical improvement, based on a CPIS score >6 on day 8[76] (GRADE score 2).

The rates of de-escalation vary among studies and adherence to guidelines for VAP is also highly variable[96,97] and obviously dependent on a high-quality microbiological diagnosis. Several studies have shown that once broad-spectrum empiric antibiotics are initiated they are rarely discontinued, even when culture results are negative[98,99] (GRADE score 1 for both). Frequently, the high proportion of patients with negative cultures who were not de-escalated appears to be influenced by the lack of specific recommendations for discontinuation of therapy. On the other hand, the adoption of precise criteria to stop therapy in culture-negative episodes of suspected VAP has shown good results[73] (GRADE score >4). In particular, antibiotic interruption should be considered if the CPIS score remains below 6 on the third day of therapy[71] (GRADE score >4). This strategy could also have an impact on the long-term development of resistance.

Recommendations

The use of a de-escalation strategy in the antimicrobial treatment of HAP based on an institutional protocol that incorporates local resistance patterns, is recommended. This strategy requires that following the initiation of an empirical broad-spectrum antibiotic therapy (based on patient risk factors and clinical presentation), the therapy be tailored to the specific pathogen(s) identified in microbiological cultures, by changing to a narrower spectrum treatment or to stop antibiotics if the diagnosis of HAP is not confirmed. There should be periodic revision and control of the strict application of the protocol (B).

Protocols for VAP management should provide recommendations for empirical therapy as well as for de-escalation and duration of therapy, which should not continue for more than 8 days in patients with a confirmed microbial etiology. We advise a ≥15-day antibiotic treatment for pneumonia caused by *P. aeruginosa* or *A. baumannii* or in the absence of clinical improvement on day 8 of treatment (B). Data in the literature are not sufficient to include MRSA in this group of microorganisms requiring a more prolonged treatment (D).

Protocols should be precise with regard to the criteria for discontinuation of antibiotic therapy if the diagnosis of pneumonia remains uncertain or negative (for example CPIS <6 at day-3 of therapy) (B).

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Conflict of interest

All members of the faculty of GISIG – M. Antonelli, M. Bassetti, F. Blasi, G. Carosi, F. Franzetti, G. Ippolito, M. Langer, F.N. Lauria, M. Moroni, E. Nicastri, and F. Scaglione – report no other potential conflict of interest except as reported in the specific section. The members of the working group have no specific conflict of interest to report.

Additional Conflict of interest

M. Bassetti has been on the speaker bureau and advisory board for Pfizer, Astellas, Novartis, Janssen, MSD, Bayer, Aventis, and Gilead. F. Franzetti has received paid expert opinion from Biogen-Dompé, Roche, Astra-Zeneca, Novartis, and Pfizer. G. Ippolito has received expert opinion fees from Pfizer. M. Langer has received honoraria for conferences/boards in the last 2 years. F.N. Lauria has received expert opinion fees from Pfizer. E. Nicastri has received paid expert opinion fees from MSD and Pfizer.

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