Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study

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Summary

Background The American Thoracic Society and Infectious Diseases Society of America provide guidelines for management of hospital-acquired, ventilator-associated, and health-care-associated pneumonias, consisting of empirical antibiotic regimens for patients at risk for multidrug-resistant pathogens. We aimed to improve compliance with these guidelines and assess outcomes.

Methods We implemented a performance-improvement initiative in four academic medical centres in the USA with protocol-based education and prospective observation of outcomes. Patients were assessed for severity of illness and followed up until death, hospital discharge, or day 28. We included patients in intensive-care units who were at risk for multidrug-resistant pneumonia and were treated empirically.

Findings 303 patients at risk for multidrug-resistant pneumonia were treated empirically, and prescribed treatment was guideline compliant in 129 patients and non-compliant in 174 patients. 44 (34%) patients died before 28 days in the compliance group and 35 (20%) died in the non-compliance group. Five patients in the compliance group and seven in the non-compliance group were lost to follow-up after day 14. Kaplan-Meier estimated survival to 28 days was 65% in the compliance group and 79% in the non-compliance group ($p=0\cdot0042$). This difference persisted after adjustment for severity of illness. Median length of stay and duration of mechanical ventilation did not differ between groups. Compliance failures included non-use of dual treatment for Gram-negative pathogens in 154 patients and absence of meticillin-resistant *Staphylococcus aureus* coverage in 24 patients. For patients in whom pathogens were subsequently identified, empirical treatment was active in 79 (81%) of 97 of patients receiving compliant therapy compared with 109 (85%) of 128 of patients receiving non-compliant therapy.

Interpretation Because adherence with empirical treatment was associated with increased mortality, we recommend a randomised trial be done before further implementation of these guidelines.

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Introduction

Hospital-acquired pneumonia is one of the most common nosocomial infections. Its high morbidity and mortality and associated long and costly hospital stays have been attributed in part to delayed use of effective antibiotics because of increasing antimicrobial resistance.[1–9] Culture-guided corrections to initially inadequate antimicrobial treatment strategies do not reduce death rates,[8,10–12] and prompt treatment of hospital-acquired pneumonia with broad-spectrum empirical antibiotics is therefore recommended.[13]

The American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) published updated guidelines[13] for treatment of hospital-acquired pneumonia and related infections in 2005. In these guidelines, the choice of empirical treatment is determined by whether patients have recognised risk factors for multidrug-resistant pathogens. Patients at risk include not only those with late-onset ventilator-associated pneumonia and hospital-acquired pneumonia, but also those with other health-care-associated pneumonias. This group includes patients who have been in hospital for 2 days or more in the preceding 90 days; reside in a nursing home or extended-care facility; receive chronic dialysis, home infusion therapy, or home wound care; have a family member infected with a multidrug-resistant organism or live in a community with a high prevalence of antibiotic resistance; recently received systemic antibiotics; or have an immunosuppressive disease or receive immunosuppression therapy.[13]

For patients at risk of infection with a multidrug-resistant pathogen, the guidelines[13] recommend empirical treatment with the following drugs: an antipseudomonal cephalosporin, carbapenem, or β-lactam and β-lactamase inhibitor; an aminoglycoside or antipseudomonal fluoroquinolone; and linezolid or vancomycin. These guidelines support the development of protocols for initial empirical antibiotic therapy to increase the likelihood of adequate coverage[14–18] and suggest antibiotic selection should be tailored to local patterns of susceptibility.

The ATS and IDSA explicitly recognise the need for guideline validation. As part of this validation, we created an initiative to improve performance in intensive-care units called Improving Medicine through Pathway Assessment of Critical Therapy in Hospital-Acquired Pneumonia (IMPACT-HAP). We aimed to assess the relation between guideline compliance and outcomes for patients in intensive care with multidrug-resistant pneumonia.

Methods

Patients

IMPACT-HAP was a multicentre initiative aimed at improving the care for patients with pneumonia in an intensive-care unit implemented in four academic medical centres in the USA: University of Louisville Medical Center (Louisville, KY), the Ohio State University Medical Center (Columbus, OH), Henry Ford Health System (Detroit, MI), and the University of Miami and Jackson Memorial Hospital (Miami, FL).

Adult patients (≥18 years of age) in participating intensive-care units were eligible for inclusion if there was clinical suspicion of evolving pneumonia with new or progressive infiltrates on chest radiograph and at least two of the following symptoms: new or increased cough or sputum production, fever, hypothermia, leucocytosis, left shift, leucopenia, or deterioration of pulmonary function. Patients were subsequently excluded from our analysis if they did not satisfy the ATS–IDSA criteria for being at risk of multidrug-resistant infection, microbiological data available at the time of diagnosis permitted pathogen-directed rather than empirical treatment, or if they were lost to follow-up within 14 days of pneumonia diagnosis. The study was approved by the institutional review board at each participating centre, which all waived the need for informed consent.

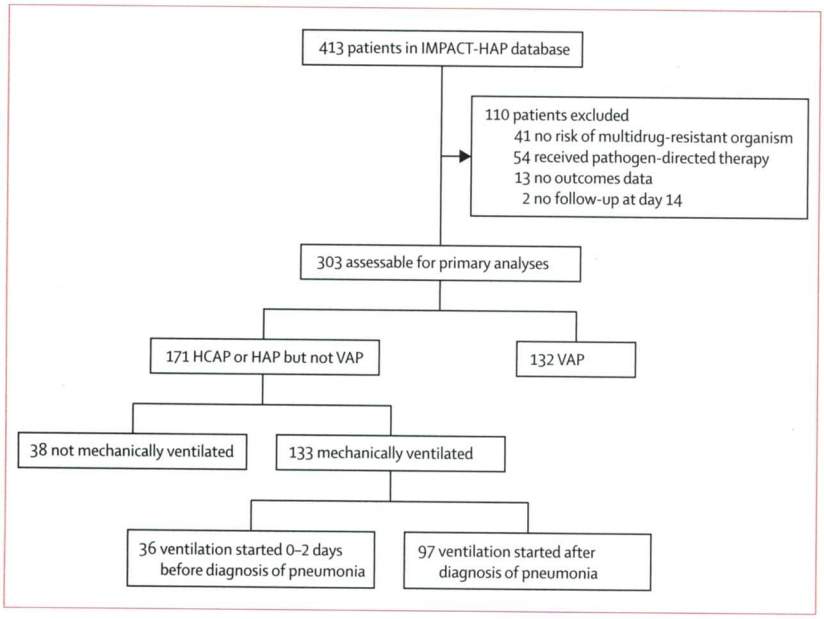

Figure 1: **Treatment characteristics of the study population**
IMPACT=Improving Medicine through Pathway Assessment of Critical Therapy. HCAP=health-care-associated pneumonia. HAP=hospital-acquired pneumonia. VAP=ventilator-associated pneumonia.

Procedures

We created a consensus diagnostic and management algorithm consistent with the ATS–IDSA guidelines.[13] From May, 2006, we disseminated this algorithm—with institution-specific antimicrobial recommendations including empirical treatment and de-escalation when feasible—to physician, nursing, clinical pharmacy, and respiratory treatment staff of participating intensive-care units through pocket cards, posters, monthly review, lectures with a standardised slide set, and personal interactions.

We included prospective monitoring to assess whether compliance with guidelines improved with education, and whether patients' outcomes improved with compliance. We collected information about patients with suspected pneumonia who were cared for in participating intensive-care units from Feb 1, 2006, depending on the timing of local institutional approval, to July 31, 2007.

We obtained data for demographics and comorbid disorders, risk factors for multidrug-resistant infection, and health-care use before diagnosis of pneumonia. Comorbid conditions were malignant disease, including any cancer apart from basal or squamous-cell cancer of the skin; end-stage lung disease, including chronic obstructive lung disease with forced expiratory volume in 1 s of less than 30% predicted or dependence on home oxygen; cardiac disease, including cardiomyopathy with an ejection fraction of less than 20% or New York Heart Association class III or IV congestive heart failure; end-stage renal disease; and liver disease with either cirrhosis or ascites. We defined immunosuppression as having received either corticosteroids or other immunomodulatory therapy equivalent to prednisone of at least 10 mg per day for more than 7 days, or chemotherapy or radiotherapy within the preceding 3 months.

At the time of pneumonia diagnosis, we assessed patients for presence of severe sepsis[19] and acuity measured with the acute physiology and chronic health evaluation (APACHE) II score[20] and modified clinical pulmonary infection score (CPIS).[21] Vital status at 14 days and 28 days after pneumonia diagnosis was established from medical records and the Social Security death index.[22] We recorded length of stay and duration of mechanical ventilation before and after diagnosis of pneumonia.

Microbiology laboratories at all four centres provided semiquantitative cultures of tracheal aspirates and either semiquantitative or quantitative cultures of bronchoalveolar lavage specimens. All culture results were reviewed at every site by the study coordinator and principal investigator to classify identified microorganisms as pathogenic or not.

Empirical antibiotic therapy was deemed compliant with guidelines[13] if, within 1 day of pneumonia recognition, therapy included the following: an antipseudomonal cephalosporin, carbapenem, or β-lactam and β-lactamase inhibitor; an aminoglycoside or antipseudomonal fluoroquinolone (in units with a high rate of carbapenem-resistant *Acinetobacter* spp, colistin was regarded as acceptable); and linezolid or vancomycin. Regimens not meeting these criteria were regarded as non-compliant. Reasons for non-compliance were classified as failure to use primary anti-Gram-negative therapy (antipseudomonal β-lactam, cephalosporin, or carbapenem); failure to use secondary anti-Gram-negative therapy (aminoglycoside, flouroquinolone, or colistin); and failure to empirically treat for meticillin-resistant *Staphlococcus aureus* (MRSA). Guideline[13] definitions were used to classify patients as having health-care-associated pneumonia, hospital-acquired pneumonia, or ventilator-associated pneumonia. Initial antibiotic regimens were classified as active if a pathogen was sensitive to at least one prescribed antibiotic. Renal insufficiency was graded with the risk-injury-failure-loss-end stage (RIFLE) classification.[23]

Statistical analysis

We compared dichotomous variables with the Fisher's exact test, and other categorical variables with the χ^2 test. We compared continuous variables with the *t* test or Wilcoxon rank-sum test and survival between groups with the log-rank test. Distributions of length of stay in hospitals and intensive-care units and duration of ventilatory support were skewed, so these data are shown as median (IQR), and other data are shown as mean (SD). We assessed development of renal dysfunction with RIFLE scores[23] and a linear test of trend. For all analyses, p less than 0·05 was significant.

We developed a propensity model for prescription of guideline-compliant empirical treatment by use of multivariate logistic regression. Potential predictors included: all risk factors for multidrug-resistant infection; comorbidities; length of hospital stay, intensive care, and mechanical ventilatory support before pneumonia; severity of illness, as characterised by APACHE II score, CPIS, and presence or absence of severe sepsis; and whether pneumonia occurred before or after the rollout of the IMPACT-HAP education programme. Predictors were selected for inclusion in the model with forward stepping with switching, requiring p less than 0·20 for every term in the model. We assessed model aptitude with the c statistic.

We assessed the relation of individual potential risk factors with guideline-compliant empirical treatment and their interactions on mortality with proportional hazards models. We calculated the hazard ratio associated with compliant treatment in the subpopulations with and without every risk factor in univariate models, and the p value for inclusion of the interaction term between each risk factor and initial therapy from the corresponding bivariate models for the whole population.

We then calculated a treatment-independent risk term for every patient, and created a proportional hazards model of survival through 28 days with the same candidate predictors as the propensity model and the propensity score itself. Potential inclusion of the propensity score in the treatment-independent risk term helps account for terms that influence both likelihood of receiving guideline-compliant empirical treatment and, separately, risk of death. We chose variables for inclusion in the model on the basis of forward stepwise selection with switching, requiring p less than 0·20 to enter or remain in the model. We calculated treatment-independent risk term for every patient from this model.

	Compliant treatment (n=129)	Non-compliant treatment (n=174)	p value
Age (years)	61 (14)	58 (18)	0·31
Previous days in hospital	7 (0–13)	6 (1–12)	0·53
Previous days in intensive-care unit	1 (0–11)	4 (0–8)	0·99
Previous days on ventilator	1 (0–9)	2 (0–7)	0·97
Previously received antibiotics	97 (75%)	98 (56%)	0·0007
Comorbid conditions			
Respiratory	30 (23%)	41 (24%)	0·99
Renal	24 (19%)	37 (21%)	0·66
Cardiac	32 (25%)	43 (25%)	0·99
Malignant disease	20 (16%)	30 (17%)	0·76
Immunosuppression	40 (31%)	39 (22%)	0·11
Severity of illness scores			
APACHE II score	21 (8)	20 (8)	0·048
CPIS	7 (2)	6 (2)	0·092
Presence of severe sepsis	117 (91%)	133 (76%)	0·001

Data are mean (SD), median (IQR), or n (%), unless otherwise stated. APACHE=acute physiology and chronic health evaluation. CPIS=clinical pulmonary infection score.

Table 1: **Baseline demographics and severity of illness**

	Compliant treatment (n=129)			Non-compliant treatment (n=174)		
	Patients	Treatment active	Deaths	Patients	Treatment active	Deaths
MRSA	27 (21%)	25 (93%)	11 (42%)	50 (29%)	38 (76%)	9 (18%)
Pseudomonas spp	33 (26%)	29 (88%)	15 (45%)	17 (10%)	14 (82%)	3 (18%)
Klebsiella spp	11 (9%)	9 (82%)	2 (18%)	16 (9%)	14 (88%)	6 (37%)
MSSA	7 (5%)	7 (100%)	0	17 (10%)	17 (100%)	1 (6%)
Acinetobacter spp	11 (9%)	5 (46%)	0	7 (4%)	4 (57%)	3 (43%)
Escherichia coli	3 (2%)	2 (67%)	2 (67%)	13 (7%)	10 (77%)	3 (25%)
Enterobacter spp	2 (2%)	2 (100%)	1 (50%)	10 (6%)	9 (90%)	3 (30%)
Polymicrobial*	25 (19%)	17 (68%)	9 (36%)	45 (26%)	33 (73%)	12 (27%)
Culture negative	30 (23%)	..	10 (33%)	40 (23%)	..	7 (18%)

Data are n (%). MRSA=meticillin-resistant *Staphlococcus aureus*. MSSA=meticillin-sensitive *Staphlococcus aureus*. *Patients are also listed by individual pathogen.

Table 2: **Frequency, treatment coverage, and deaths from the most common pathogens, grouped by empirical treatment compliance**

	APACHE II score ≤20		APACHE II score >20		All patients	
	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant
MRSA	0/0	0/2	1/1	2/4	1/1	2/6
Pseudomonas	0/1	0/1	1/3	0/0	1/4	0/1
Klebsiella	0/2	0/0	0/1	0/0	0/3	0/0

Data are number of deaths/number of infections. APACHE=acute physiology and chronic health evaluation. MRSA=meticillin-resistant *Staphlococcus aureus*.

Table 3: **Most common pathogens identified by blood culture within –1 to 1 day after start of empirical treatment**

	Regression coefficient	Odds ratio (95% CI)
Intercept	–2·922	0·054 (0·015–0·192)
History of end-stage liver disease (yes/no)	–1·358	0·257 (0·069–0·956)
Days already spent in intensive-care unit	0·025	1·025 (0·999–1·052)
Before versus after rollout of the education programme (yes/no)	0·652	1·920 (1·122–3·286)
Previous antibiotic therapy (yes/no)	0·725	2·065 (1·201–3·548)
Presence of severe sepsis (yes/no)	1·128	3·090 (1·496–6·384)
Age (years)	0·011	1·011 (0·996–1·027)

Table 4: **Propensity model for guideline-compliant empirical treatment**

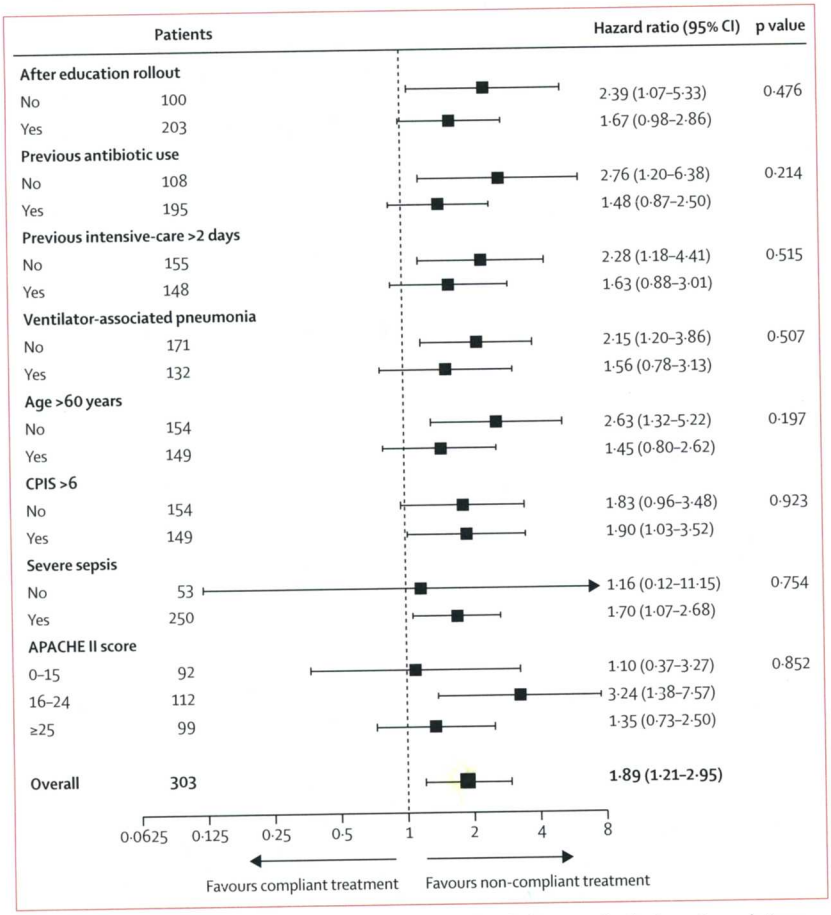

Figure 2: **Guideline-compliant empirical treatment outcomes for 28-day mortality for key subpopulations**
CPIS=clinical pulmonary infection score. APACHE=acute physiology and chronic health evaluation.

The coefficient for treatment-independent risk term is unity in a univariate model.

We calculated risk-adjusted hazard for death with guideline-compliant empirical treatment across the whole population by including initial therapy and the treatment-independent risk term in a bivariate proportional hazards model. Equivalent analyses were done for the subpopulations infected with Gram-negative pathogens, Gram-positive pathogens, *Pseudomonas* spp, and MRSA, for patients with polymicrobial infections, and patients with negative cultures. All statistical analyses were done with NCSS 2004 (Kayesville, UT, USA) and PASW Statistics 17.0 (Chicago, IL, USA).

Role of the funding source

Investigators who were employed by the sponsor participated in the processes of study design and data interpretation, and contributed to editing of the report. Investigators from sites in Louisville and Miami (but not the sponsor) had full access to data, and investigators from sites in Miami did the data analysis. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

413 patients with pneumonia were in the IMPACT-HAP database. 303 had risk factors for multidrug-resistant pneumonia and were eligible for this analysis, and most required mechanical ventilation during their disease course (figure 1). All patients satisfying criteria for health-care-associated pneumonia also satisfied criteria for hospital-acquired pneumonia. 129 patients received guideline-compliant[13] empirical antibiotic treatment, whereas 174 patients received non-compliant treatment. Reasons for non-compliance were failure to use a secondary anti-Gram-negative drug (154 patients) or, less commonly, failure to use either a primary anti-Gram-negative drug (24 patients) or anti-MRSA drug (24 patients).

Guideline compliance with empirical treatment rose modestly during the IMPACT-HAP education programme, from 33 (33%) of 100 cases before rollout to 96 (47%) of 203 cases after rollout (p=0·019). 24 (24%) patients died by day 28 in the period before rollout (Kaplan-Meier estimated survival 76%), whereas 55 (27%) died by day 28 after rollout (Kaplan-Meier estimated survival 72%; p=0·46).

Differences in comorbidities and length of stay before diagnosis of pneumonia between groups were small (table 1). At the time of pneumonia diagnosis, patients receiving compliant empirical treatment were more likely to meet criteria for severe sepsis than were those in the non-compliant group (p=0·0012) and had slightly higher APACHE II scores (p=0·048).

We obtained microbiology samples suitable for assessment from 295 (97%) of 303 patients. At least one organism suspected of being a pneumonia pathogen was

identified in 225 (76%) of these 295 patients (table 2). Empirical treatment was active against all identified pathogens in 79 (81%) of 97 patients receiving initial compliant treatment and 109 (85%) of 128 patients receiving initial non-compliant treatment (p=0·47). For the most common pathogens, we report the frequency, coverage, and number of deaths grouped by empirical treatment (table 2). Webappendix p 1 shows the treatment activity for the most common multidrug-resistant pathogens. We drew blood cultures from over 80% of patients before antibiotics were initiated for treatment of pneumonia. At assessment of blood culture results from the day before until the day after the diagnosis of pneumonia, 26 patients had positive cultures thought to be pathogenic. Table 3 shows classification of the most common pathogens by compliance of empirical treatment with guideline recommendations and severity of illness.

33 (26%) of 129 samples from patients treated with a guideline-compliant empirical regimen had eventual recovery of *Pseudomonas aeruginosa* as a pathogen, compared with 17 (10%) of 174 (p=0·0003) of those not on guideline-compliant treatment. In patients with *Pseudomonas* spp infection, empirical treatment was active against all identified pathogens in more than 80% of patients and did not differ between patients in compliant or non-complian t groups (p=0·68; table 2).

Factors positively associated with use of guideline-compliant empirical treatment in the propensity model included days already spent in intensive care, previous receipt of antibiotics, pneumonia occurring after rollout of the education programme, presence of severe sepsis, and age (table 4). End-stage liver disease was included in the model and predicted non-compliance. The c statistic for the propensity model was 0·70.

44 of 129 (34%) patients receiving compliant empirical treatment died by 28 days, with five lost to follow-up after 14 days. 35 of 174 (20%) patients receiving non-compliant treatment died by 28 days, with seven lost to follow-up after 14 days. The Kaplan-Meier estimate of survival to 28 days was 65% in patients treated with a compliant regimen and 79% in those receiving a non-compliant regimen (p=0·0042). This survival benefit did not vary with key factors presumed to be related to either mortality or guideline compliance (figure 2). Exclusion of the nine patients who received colistin did not change this result.

The non-treatment proportional hazards model of survival included APACHE II score, malignant disease, vascular disease, presence of severe sepsis, days already spent in intensive care, and hospital admission for 5 days or more. These terms were combined and weighted by their regression coefficients, to form the treatment-independent risk term. The propensity for prescription of guideline-compliant empirical treatment did not contribute to this model.

In bivariate proportional hazards analysis, which also included the treatment-independent risk term, use of ATS–IDSA-compliant empirical treatment remained an independently significant risk factor for death (hazard ratio 1·56, 95% CI 1·00–2·44, p=0·0498), whereas the coefficient for the treatment-independent risk term remained close to unity (0·97, standard error 0·14). When analyses were restricted to specific pathogens, guideline compliance never appeared beneficial (figure 3).

No association between guideline-compliant initial therapy and duration of ventilatory support, length of stay in intensive-care, or length of stay in hospital after diagnosis of pneumonia was observed (table 5). These results were unaffected by exclusion from analysis of patients who died within 14 days of pneumonia diagnosis, who might have decreased use of hospital resources because of death rather than recovery.

See Online for webappendix

Patients who met criteria for ventilator-associated pneumonia had APACHE II scores of 19 (SD 7) compared with 22 (8) for those who did not meet criteria (p=0·015), without significant differences in CPIS or presence of severe sepsis. Survival through 28 days was much the same at 75% in patients with ventilator-associated pneumonia

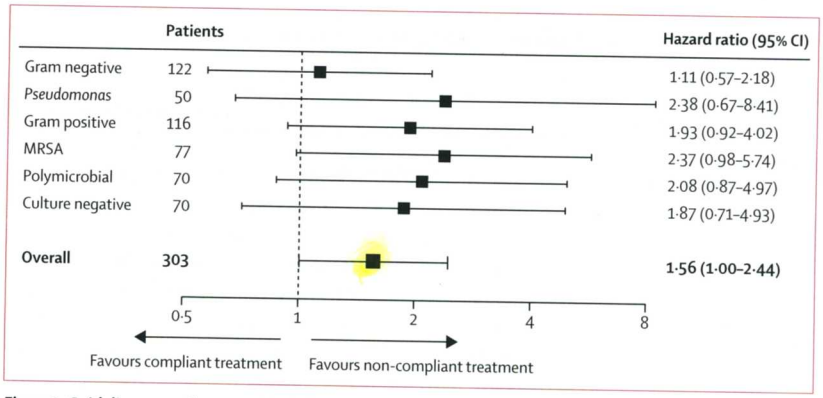

Figure 3: **Guideline-compliant empirical treatment outcomes for 28-day mortality, grouped by pathogen and adjusted for treatment-independent risk**
MRSA=meticillin-resistant *Staphlococcus aureus*.

	Compliant treatment (n=129)	Non-compliant treatment (n=174)	p value
Survival through day 28 (total population)	65% (3)	79% (4)	0·004
Baseline CPIS <7	68% (6)	80% (4)	0·063
Baseline CPIS ≥7	63% (6)	78% (5)	0·037
Survival through day 28 (patients with *Pseudomonas* spp infection*)	55% (9)	82% (9)	0·064
Resource use, after pneumonia (days)			
Mechanical ventilation support (total population)	8 (3–15)	9 (2–18)	0·44
Length of stay in ICU (total population)	12 (7–22)	13 (5–20)	0·57
Length of stay in hospital (total population)	16 (9–28)	17 (10–26)	0·52
Mechanical ventilation support (survivors to day 14)	8 (2–18)	9 (2–18)	0·81
Length of stay in ICU (survivors to day 14)	14 (7–23)	13 (5–21)	0·15
Length of stay in hospital (survivors to day 14)	18 (11–32)	18 (10–28)	0·55

Data are Kaplan-Meier % (SE) estimates of survival or median (IQR), unless otherwise stated. ICU=intensive-care unit.
*We isolated *Pseudomonas* spp for 50 patients (33 patients in the compliant group and 17 in the non-compliant group).

Table 5: **Treatment outcomes, grouped by empirical treatment compliance**

	Pseudomonas group (n=50)	Non-*Pseudomonas* group (n=245)	p value
Previous days in hospital	9 (0–22)	6 (0–11)	0·07
Previous days in an intensive-care unit	7 (0–18)	2 (0–8)	0·02
Previous days on a ventilator	5 (0–20)	1 (0–7)	0·002
Severity of illness scores			
APACHE II score	21 (8)	21 (8)	0·97
CPIS	6 (2)	6 (2)	0·69
Presence of severe sepsis	39 (78%)	203 (83%)	0·42

Data are median (IQR), mean (SD), or n (%), unless otherwise stated. APACHE=acute physiology and chronic health evaluation. CPIS=clinical pulmonary infection score.

Table 6: **Baseline characteristics and severity of illness for patients with pneumonia related to *Pseudomonas* compared with patients with pneumonia not related to *Pseudomonas***

	Colistin (n=9)	Aminoglycoside (n=101)	Neither colistin nor aminoglycoside (n=158)
None	3 (33)	63 (63)	116 (73)
Risk	1 (11)	16 (16)	17 (11)
Injury	4 (44)	13 (13)	7 (4)
Failure	1 (11)	9 (9)	18 (11)

Data are n (%). Risk, injury, and failure form part of the RIFLE classification[23] of increasing severity of acute renal dysfunction, which also includes loss and end-stage kidney disease, which are not reported here because they are not applicable. RIFLE=risk-injury-failure-loss-end stage.

Table 7: **Secondary Gram-negative antibiotic use and development of renal dysfunction, by RIFLE classification group**

and 71% in others (p>0·5). A proportional hazards model including the treatment-independent risk term, compliance with empirical treatment, ventilator-associated pneumonia, and an interaction term for ventilator-associated pneumonia found that guideline compliance was associated with increased mortality, with no significant contribution from the ventilator-associated pneumonia term or its interaction with guideline compliance.

We did additional analyses because patients with pneumonia associated with *Pseudomonas* spp were more likely to have received guideline-compliant empirical treatment than were other registry patients. Compared with the rest of the IMPACT-HAP population, patients with pseudomonas-related pneumonia had longer lengths of stay before diagnosis, but much the same severity of illness at time of diagnosis (table 6). Although patients who had *Pseudomonas* spp isolated and received guideline-compliant initial therapy had higher APACHE II scores than did those who received non-compliant therapy (22 [SD 8] versus 18 [6], p=0·057), bivariate proportional hazards analysis done on the basis of the treatment-independent risk term and regimen compliance restricted to this population did not suggest that compliant empirical treatment was beneficial (hazard ratio with compliance 2·4, 95% CI 0·7–8·4; figure 3).

Compared with the number of patients who received empirical initial therapy for pneumonia, few patients received pathogen-directed therapy (figure 1). Of 54 patients receiving pathogen-directed therapy, 45 ultimately had a pathogen recovered. 28-day survival was 83% for these patients, which was somewhat better than that noted for those treated empirically. The prescribed regimen was active against all identified pathogens in 43 of 45 patients. None of these patients received a regimen that would have been regarded as guideline compliant had it been empirical.

The antibiotics recommended in present guidelines[13] potentially have nephrotoxic effects. 268 patients did not require renal-replacement therapy at the time of pneumonia diagnosis and had serial measurements of serum creatinine. Use of either colistin or an aminoglycoside was associated with a greater risk for deterioration of renal function in this group (p=0·001; table 7). By contrast, no such relation was seen with vancomycin use. Survival until day 28 decreased with increasing RIFLE severity of renal insult and was 76% with none, 73% with risk, 63% with injury, and 61% with failure (p=0·038).

Discussion

In our cohort study, compliance with the ATS–IDSA guidelines[13] was associated with increased mortality.

Present recommendations[13] for management of pneumonia in patients at risk for multidrug-resistant pathogens call for prompt broad-spectrum empirical treatment. This recommendation is supported by the consistent finding that delaying of effective antibiotic therapy is associated with increased mortality.[5,8,10] The ATS–IDSA guidelines recommend that patients at risk should initially receive a combination of antibiotics with a sufficiently broad spectrum so that at least one drug will be active against any likely pathogen. Despite the acknowledged absence of high-level evidence, dual Gram-negative coverage was believed to be warranted.

The guidelines[13] reference a meta-analysis[24] of sepsis studies concluding that combination β-lactam and aminoglycoside regimens were associated with higher rates of clinical failure than was β-lactam monotherapy, did not lead to better outcomes among patients with *Pseudomonas* spp infections or prevent the emergence of resistance, and were associated with nephrotoxic effects. Since the publication of these guidelines, a randomised trial[25] and two additional meta-analyses of empirical antibiotic therapy for patients with ventilator-associated pneumonia have reported that monotherapy was at least as efficacious as combination therapy.[26,27]

The findings of our analyses are echoed in clinical practice. We noted that physicians, despite the educational efforts of IMPACT-HAP to encourage dual therapy for patients with high risk of multidrug-resistant infection, did not prescribe dual Gram-negative initial coverage in most cases. Clinicians used more antibiotics, and were more likely to comply with ATS–IDSA guidelines in patients who had comorbidities, long stay before diagnosis of pneumonia, severe sepsis, and high severity

scores. The differences in baseline characteristics and severity of illness between treatment groups were small. Furthermore, after adjustment for these differences, selection of guideline-compliant empirical treatment remained associated with decreased survival.

ATS–IDSA guidelines recommend that the broad-spectrum empirical treatment be de-escalated when possible, on the basis of clinical response and microbiological data. The goal of de-escalation, as put forth within the guidelines, is to limit the emergence of resistance in hospitals.[13] The existing limited trials of either early discontinuation or policies encouraging early discontinuation of empirical treatment do not make a compelling case for mortality reduction associated with this strategy.[14,17,28] Because recommendations for de-escalation incorporate a component of clinical judgment, adherence is inherently difficult to quantify. However, for our population, among patients receiving a second Gram-negative agent without documented acinetobacter or pseudomonas infection, the secondary drug was discontinued by day 3 in more than 50% of patients, and by day 5 in more than 75%. Equally, in patients prescribed either vancomycin or linezolid who were not subsequently confirmed to have MRSA infection, 48% had the drug discontinued by day 3.

A potential explanation for the increased mortality associated with guideline-compliant empirical regimens was antibiotic-specific toxic effects. Colistin and aminoglycoside use were associated with acute deterioration of renal function. Neurotoxic effects have been described with aminoglycosides,[29–31] colistin,[32] and fluoroquinolones.[33] Aminoglycosides contribute to critical illness polyneuropathy and myopathy. Prolongation of fluoroquinolone-induced QT interval can lead to life-threatening ventricular arrhythmias.[34]

Our study has limitations. IMPACT-HAP was an observational study of patients in intensive-care units, not a randomised trial of treatment strategies. As such, IMPACT-HAP did not dictate prescription practice. Clinicians individualised empirical antibiotic prescribing on the basis of patients' clinical complexity and severity of illness. Physicians probably used more antibiotics (and therefore were more likely to comply with the guidelines) for patients with severe sepsis or those with high APACHE II scores. However, these differences, although statistically significant, were clinically small. For example, the observed one point difference in APACHE II scores would be consistent with a mortality difference of 2–5%. Even after adjustment for severity differences, there was no suggestion that guideline compliance afforded better outcomes than did non-compliance. IMPACT-HAP studied only patients in intensive-care units, most of whom were receiving mechanical ventilation. Therefore, our results might not be applicable to patients with health-care-associated and hospital-acquired pneumonia in general inpatient wards.

Panel: Research in context

Systematic review

We searched the Medline database for studies assessing guidelines for treatment of ventilator-associated pneumonia, hospital-acquired pneumonia, health-care-associated pneumonia, or nosocomial pneumonia. No studies have prospectively assessed the outcomes of multicentre efforts to implement the most recent versions of the American Thoracic Society and Infectious Diseases Society of America guideline, which recommends a combination of two drugs that are active against Gram-negative pathogens and one against meticillin-resistant *Staphylococcus aureus* for patients at risk of infection with a multidrug-resistant pathogen. Since the guideline's publication in 2005, three meta-analyses[24,26,27] and one randomised trial[25] have failed to show benefit with combination Gram-negative therapy, and other guidelines' writing groups have suggested dual Gram-negative therapy is not warranted.

Interpretation

Our results further question the need for combination Gram-negative empirical treatment for all patients with pneumonia, even those who are severely ill and evidently at high risk for multidrug-resistant pathogens. A large randomised trial is needed to resolve this issue.

The IMPACT-HAP database might not capture all the factors that influenced prescribing practice and affected mortality. For example, although we recorded APACHE II scores, which account for hypotension, many patients already in intensive care might have this physiological state ameliorated by vasopressors, which are not captured by the APACHE II score. IMPACT-HAP did not obtain data specifically for septic shock at the time when antibiotics were prescribed for pneumonia. The database did record the presence of either hypotension or raised lactate within the 24 h before diagnosis of pneumonia. Although the presence of these factors might have been due to septic shock, raised lactate was uncommon and brief periods of hypotension (such as commonly occur with induction, initiation of analgesia, and sedation) would be captured and might have resolved with fluids or time. We are therefore cautious about interpreting these data as presence or absence of septic shock at the time antibiotics were prescribed or delivered, the usual interpretation of the term in studies of this type. However, addition of a composite variable of hypotension or increased lactate to the treatment independent risk term did not change our main findings, with a hazard risk for death associated with compliant empirical treatment of 1·55.

Alternative approaches to analysis of our data do not lead to different conclusions. For example, the hazard risk for death associated with guideline-compliant empirical treatment was 1·93 when model building

considered all of the variables available for the treatment-independent risk term, whether ventilator-associated pneumonia criteria were satisfied, all species data, centre, the shock term, and empirical treatment (webappendix p 2). Although not impossible, other unmeasured factors are probably not of sufficient weight to mask a beneficial effect of guideline-compliant empirical treatment and make it seem inferior. However, the only way to fully resolve this question is a randomised, controlled trial.

The guidelines recognise immunosuppressive disease or therapy as risk factors for multidrug-resistant pathogens. Conversely, they were not intended to apply to patients with severe immunosuppression, characterised as "immunosuppressed by human immunodeficiency virus (HIV) infection, hematologic malignancy, chemotherapy-induced neutropenia, organ transplantation, and so on."[13] This risk is, in many cases, a matter of judgment and degree; the guidelines' silence with regard to their own applicability in the case of corticosteroids (the most commonly used immunosuppressive therapy) speaks to this difficulty.

Our dataset included ten patients with AIDS (all with normal peripheral white blood cell count), 19 patients who had received chemotherapy (but only two with peripheral white blood cell count less than 2000 per µL), eight patients who had received radiation therapy (all with normal peripheral white blood cell counts [3600–11100 cells per µL]), and 55 who had received corticosteroids. Removal of these patients from all analyses modestly increases the strength of association of guideline-compliant empirical treatment with death. The treatment-independent risk term was rebuilt without these patients (and with and without the potential use of the shock term, which did not enter the model when available). The risk ratio associated with guideline-compliant treatment in bivariate analysis including this new treatment-independent risk term was 1·88 (p=0·026), which was slightly higher than we report for the entire population (1·56).

Despite our hopes to the contrary, we found that the use of guideline-compliant empirical treatment in patients in intensive-care units who were at risk for multidrug-resistant pathogens was associated with increased mortality. Data from a prospective performance improvement project, intended to account for prognosis, does not otherwise explain this finding. We therefore recommend that the planned, revised ATS–IDSA guidelines be reassessed before widespread implementation. Since the most common reason for non-compliance was failure to use a secondary anti-Gram-negative drug, we suggest a comparison of regimens employing MRSA treatment and single versus dual Gram-negative coverage.

Contributors

All authors contributed equally to the study design, data collection, and analyses, and have seen and approved the final manuscript.

IMPACT-HAP investigators

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Conflicts of interest

DHK has received research support from Pfizer, and has been a consultant and member of the speakers' bureau of Pfizer, Astellas, Cubist, and GlaxoSmithKline. JEM has served on advisory boards for Madcat Healthcare, Pfizer, Astellas, Merck, and received educational grants from Fallon Medica. MJZ has received research support from Astellas, Cubist, and Johnson and Johnson, and is on the speakers' bureaux of Astellas and Cubist. JAR has received research support from and is a consultant for Pfizer, and has received lecture honoraria from Pfizer, Merck, and Wyeth. KDF and EGS are employees of Pfizer. All other authors declare that they have no conflicts of interest.

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Nosocomial pneumonia: de-escalation is what matters

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The American Thoracic Society guideline[1] for management of hospital-acquired, ventilator-associated, and health-care associated pneumonia in adults is probably one of the most authoritative document for clinicians caring for patients with nosocomial pneumonia worldwide. This authority stems from the interpretation of available data for a complex issue provided by an experienced group of clinical scientists, resulting in a seemingly very differentiated and balanced set of useful recommendations. Nevertheless, the conceptual framework and recommended treatment regimens are chiefly an expert-based rather than an evidence-based statement. In *The Lancet Infectious Diseases* today, the guideline faces its worst-case scenario: adherence for treatment of patients with risk factors for multidrug-resistant (MDR) pathogens is associated with increased mortality.[2] Moreover, the investigators recommend stopping of guideline implementation until a randomised trial is done.

According to the guideline,[1] patients with risk factors for MDR pathogens should receive a triple regimen, with dual coverage of Gram-negative pathogens and meticillin-resistant *Staphlococcus aureus* (MRSA). The present study[2] reports that, in patients in whom pathogens were subsequently identified, adherence to this recommendation resulted in a 28-day mortality of 35% in patients receiving compliant treatment and 21% in those receiving non-compliant therapy, even after adjustment for severity of illness. What reasons could account for this counterintuitive finding?

First, because triple coverage aims to include at least one drug active against an MDR pathogen to avoid excess mortality of initially inadequate treatment, comparison of the proportion of treatment regimens active against underlying MDR pathogens in both groups was crucial. However, in the study,[2] initial empirical treatment was active in 81% of patients receiving compliant treatment but 85% of the non-compliant group. Hence, a difference favouring adherent treatment was not to be expected. Coverage of MDR meticillin-sensitive *S aureus* (MSSA), Gram-negative enteric bacteria, and *Pseudomonas aeruginosa* was 100% in the non-compliant group; however, as shown in the paper's webappendix coverage of other MDR pathogens was lower in the compliant group (17 cases, 59% *vs* 94%), a finding that remains uncommented.

For individual pathogens, mortality in the compliant group was substantially higher than in the non-compliant group for MRSA and *Pseudomonas* spp, the reverse was true only for *Acinetobacter* spp and

Klebsiella spp. Patients in the compliant group with other pathogens and those who had negative cultures had almost double the mortality. Thus, differences in mortality cannot be related to the coverage of the regimen applied in patients with MSSA, MRSA, Gram-negative enteric bacteria, and *P aeruginosa*. Differences might be related to other pathogens or to patients without an identified pathogen. Again, the authors do not comment.

Second, differences between groups might be explained by timing of antimicrobial therapy. In patients with septic shock, initiation within 1 h of diagnosis is crucial for survival. Timeliness of treatment initiation was not assessed in this study.

Third, excess mortality might be related to treatment toxicity of triple coverage. Renal toxic effects are the main issue in this regard because they are the main acute toxic effect of aminoglycosides, colistin, MRSA-active drugs, and quinolones. Moreover, renal failure is an independent determinant of mortality in intensive-care units, with an increment of serum creatinine of 0·3 mg per dL or more in 48 h predicting clinical outcome.[3] In today's study,[2] use of aminoglycosides and colistin was associated with an increased risk of deterioration of renal function. Furthermore, survival decreased with increasing risk-injury-failure-loss-end stage (RIFLE) score severity of renal insult. However, the number of patients with renal injury and failure on aminoglycosides and colistin was low, not consistently different from the group not receiving these drugs, and seemingly not high enough to affect outcomes.

So with detailed review, the available data might explain equivalence, but not excess mortality. Therefore, concerns about the study methods need to be addressed.

A crucial issue is whether adjustment for risk of death was truly achieved. In particular, severity of illness was assessed by acute physiology and chronic health evaluation (APACHE) II score, which is of questionable validity as a stratification technique. The decision to include only cancer and end-stage lung, heart, renal, and liver disease as comorbidities accounts for the high prognostic effect of these conditions but might not identify important differences between advanced but not end-stage conditions. Moreover, septic shock and functional status, both crucial in terms of prognosis, were not systematically assessed.

Another concern is the failure to follow a standard of microbial investigation, which might have biased the analysis of adequacy of antimicrobial treatment.

The disregard of treatment de-escalation in classification of compliance is perhaps the most serious argument against Kett and colleagues' analysis.[2] The authors state that in patients receiving secondary Gram-negative coverage but without pseudomonas or acinetobacter infection, the secondary agent was discontinued by day 3 in more than 50% of patients and by day 5 in 75% of patients. Similarly, MRSA coverage was discontinued by day 3 in 48% of patients without MRSA. Nevertheless, this means that around 25–50% of patients classified as compliant were actually non-compliant to guidelines in a strict sense. This misclassification is important to note because the triple-coverage approach for patients at risk of MDR is invariably linked to the notion of de-escalation of antimicrobial treatment according to microbial results.

Taken together, the validity of today's analysis[2] is subject to controversy. In my view, it does not provide a convincing link between pathogens (particularly MDRs), applied antimicrobial treatments, the rate of appropriate and inappropriate treatments according to pathogens isolated, the effect of treatment adequacy on clinical outcome (adjusted for severity and comorbidity), and the effect of treatment-related toxic effects on outcomes.

However, the recommended triple approach is not necessarily correct: initial dual coverage might be better in patients with septic shock and those with *P aeruginosa* bacteraemia and ventilator-associated pneumonia. In these patients, de-escalation (ie, monotherapy) according to culture and susceptibility results is adequate.[4,5] Additionally, combination therapy can improve the appropriateness of empirical therapy in episodes attributed to extended-spectrum β-lactamase-producing or AmpC-producing Enterobacteriaceae and *P aeruginosa*.[6] Conversely, superiority of dual coverage of Gram-negative enteric bacteria in haemodynamically stable patients is unresolved.[7–10] β-lactam and aminoglycoside combinations have been associated with a worse outcome, but the studies used dosage schedules now recognised as inadequate.[11] The rationale for regular empirical MRSA coverage remains questionable, at

least in patients who are haemodynamically stable. Overall, the triple-coverage approach in patients at risk of MDR seems insensitive to local variations of MDR prevalence and does not account for considerations about treatment restrictions in elderly and severely disabled patients. In particular, the notion of health-care-associated pneumonia is poorly supported by available data, and implies overtreatment in many patients.[12]

All patients with septic shock, and probably severe sepsis, should receive dual coverage or triple coverage if MRSA is a concern. Whether all haemodynamically stable patients with nosocomial pneumonia need such a wide coverage is questionable; at least, de-escalation treatment is mandatory, since it reduces selection pressure, organ toxic effects, and saves money. After all, de-escalation is what matters. The definition of non-adherence to American Thoracic Society guidelines should not read "less than triple therapy" but rather "less than long-term prognosis and risk-adjusted broad coverage and de-escalation according to culture and susceptibility results".

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Malaria control in pregnancy: still a long way to go

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Pregnant women, especially those pregnant for the first time, are at increased risk of more frequent and more severe malaria infections than are non-pregnant women.[1–3] In endemic areas, malaria in pregnancy is a major preventable cause of maternal morbidity and poor birth outcomes. Use of insecticide-treated nets can decrease maternal anaemia and parasitaemia, resulting in improved pregnancy outcomes.[4,5] Furthermore, the use of intermittent preventive treatment with sulfadoxine–pyrimethemine during pregnancy can reduce maternal anaemia, placental malaria, and the number of infants born with low birthweight.[6,7]

In the *Lancet Infectious Diseases* today, Anna Maria van Eijk and colleagues[8] report the progress of coverage with malaria control interventions in pregnant women in sub-Saharan Africa. The report is a substantial effort on the part of the investigators to compile data from all the countries in the sub-Saharan region. The findings emphasise that, although progress has been made in the scaling up of malaria-control interventions, the goals set by the Roll Back Malaria Partnership

Guidelines for hospital-acquired pneumonia and health-care-associated pneumonia: a vulnerability, a pitfall, and a fatal flaw

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The 2005 American Thoracic Society and Infectious Disease Society of America's guidelines for pneumonia introduced the new category of health-care-associated pneumonia, which increased the number of people to whom the guidelines for multidrug-resistant pathogens applied. Three fundamental issues inherent in the definition of hospital-acquired pneumonia and health-care-associated pneumonia undermined the credibility of these guidelines and the applicability of their recommendations: a vulnerability, a pitfall, and a fatal flaw. The vulnerability is the extreme heterogeneity of the population of patients. The fatal flaw is the failure to accurately diagnose hospital-acquired pneumonia and ventilator-associated pneumonia; inability to distinguish colonisation from infection in respiratory-tract cultures renders the guidelines inherently unstable. The pitfall is spiralling empiricism of antibiotic use for severely ill patients in whom infection might not be present. A vicious circle of antibiotic overuse leading to emergence of resistant microflora can become established, leading to unnecessary use of empirical broad-spectrum combination antibiotics and increased mortality. Controlled studies now show that administration of broad-spectrum combination antibiotic therapy can lead to increased mortality in uninfected patients. Proposed solutions include the use of individualised assessment of patients. Health-care-associated pneumonia should be broken down into several distinct subgroups so narrow-spectrum antibiotic therapy can be used. Emphasis should be placed on defining the microbial cause of the pneumonia rather than reflex administration of empirical combination therapy.

Introduction

In 2005, the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) published guidelines[1] for management of adults with hospital-acquired pneumonia. A new category, defined as health-care-associated pneumonia, was introduced that broadened the scope of the guidelines to include ambulatory patients who were regarded as likely to have multidrug-resistant pathogens.

Unlike guidelines for community-acquired pneumonia,[2] confirmation of the approach and acceptance by clinicians of the 2005 hospital-acquired pneumonia guidelines has been marginal.[3,4] Shigeki Fujitani and I[5] pointed out that the 2005 guidelines were laudable in their intent, although poor in execution. Ewig and colleagues issued a reasoned critique[6] of the 2005 guidelines that was notable for its comprehension and backed by a critical and insightful review of the published work.

In this issue of *The Lancet Infectious Diseases*, in a prospective study of compliance versus non-compliance to the 2005 guidelines,[1] Daniel Kett and colleagues[7] report that 28-day mortality was significantly higher in patients who received antibacterial therapy classified as compliant than in those whose treatments were non-compliant. Compliance was essentially the use of combination broad-spectrum treatment whereas non-compliance was a surrogate for monotherapy. The reason and mechanism for this surprising result is unclear, but this finding was consistent in the overall group and numerous subgroups. Moreover, the higher mortality for the combination group compared with the monotherapy group could not be ascribed to the adverse effects of aminoglycoside therapy, which is often used as a component of combination antibacterial agent therapy.

History of pneumonia guidelines

One of the most successful and influential of all medical guidelines was the consensus piece for community-acquired pneumonia, first initiated 17 years ago by Thomas Marrie and subsequently chaired by Lionel Mandell, Michael Niederman, and John Bartlett. Therefore, formulation of guidelines for hospital-acquired pneumonia was logical and tempting, and, in 1996, the ATS–IDSA did so. New additions to the 2005 guidelines included newer definitions of nosocomial, hospital-acquired, ventilator-associated, and health-care-associated pneumonia. Problems immediately surfaced: the classifications were imprecise,[5] not easily generalisable, and the definitions varied from country to country. Marginal data, cherry-picking, and the small number of studies on which they were based weakened the validity of the 2005 guidelines.[6]

The foundation for initial community-acquired pneumonia guidelines[2] was a prospective observational study,[8] based on intensive microbiology for all patients; this study uncovered new microbial causes that were underappreciated at the time, including *Chlamydophila pneumoniae* and *Legionella* spp. A quantitative analysis was also done for the outcome of patients admitted to hospital that suggested that factors could be identified to minimise hospital admissions without adversely affecting outcomes.[9] Numerous confirmatory observational studies from other hospitals

and other countries strengthened the conclusions of the community-acquired pneumonia guidelines.[2,10–13]

With time, adherence to guidelines for community-acquired pneumonia improved outcomes in this group of patients. Most importantly, hospital pharmacies developed clinical pathways and the US Centers for Medicare and Medicaid Services and Joint Commission developed performance measures that mandated doctors' adherence to the guidelines. Other countries and societies issued their own guidelines for community-acquired pneumonia—imitation is the sincerest form of flattery. Of note was that therapy recommendations derived from the guidelines were different from existing practice at the time of its introduction. It was a credit to the pharmaceutical industry that subsequent development included new respiratory-tract macrolides and quinolones that were active against all the common pathogens of community-acquired pneumonia; this advance allowed a feasible and straightforward strategy of empirical antibiotic therapy. Could this success be transferred to guidelines for hospital-acquired pneumonia and health-care-associated pneumonia? Unfortunately, it could not.

Health-care-associated pneumonia

The vulnerability of the 2005 guidelines for health-care-associated pneumonia was the extreme heterogeneity of the population. This heterogeneity resulted from the desire of the guidelines committee to devise a straightforward approach of broad-spectrum empirical antibiotic therapy for the largest possible group of patients. Haemodialysis patients were lumped together with patients in nursing homes. Even within the category of patients in nursing homes, substantial variation existed. For example, the functional status of patients ranged from ambulatory to bedridden,[6] and underlying diseases now ranged from psychiatric problems to immunosuppressive disorders.

The key to selection of appropriate antibiotics depends on accurate identification of pathogens. The fatal flaw of any of the guidelines for nosocomial pneumonia involves the traditionally difficult issue of colonisation versus pathogenicity for microbes isolated from patients' respiratory secretions.

Oropharyngeal colonisation by Gram-negative bacilli is commonplace in patients admitted to hospitals, especially in intensive-care units. For intensive-care unit pneumonia, the pathogens are more diverse because of overgrowth of normal flora by Gram-negative bacilli. Moreover, intense antibiotic use promotes the emergence of resistant organisms. Because it is difficult to distinguish colonising organisms from infecting organisms, the definitive identification of the true pulmonary pathogens has always been problematic in hospital-acquired pneumonia. Colonisation rather than pathogenicity remains a complex issue.[14] The gold standard for definition of hospital-acquired pneumonia and ventilator-associated pneumonia is contentious. The best validated gold standard remains the seminal study by French investigators of patients with pneumonia in 31 intensive-care units.[15] An invasive procedure (bronchoalveolar lavage or protected specimen brush) plus quantitative criteria of cultures was used to distinguish pathogenicity from colonisation. Nevertheless, consensus on this criterion is not universal.[16] The logistics of an invasive procedure and necessity for the procedure before antibiotics can be given were also obstacles to widespread application. So, definitive identification of respiratory pathogens involved in hospital-acquired pneumonia remains elusive, despite the use of invasive diagnostic procedures and the advent of biomarkers of inflammation.

Because of the fatal flaw in making of an accurate diagnosis of intensive-care unit pneumonia and the inherent inability to separate uninfected colonised patients from infected patients, it is probable that a notable number of uninfected patients received unnecessary broad-spectrum combination therapy in Kett and colleagues' study.[7] I suggest that this unnecessary treatment might be the basis for the increased mortality given the widespread incentive to clinicians for overtreatment. At least three prospective controlled comparative studies have shown that giving broad-spectrum antibiotics to uninfected patients leads to significantly increased mortality.[15,17,18]

The presence of meticillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* poses special dilemmas for empirical therapy. These two pathogens cause an imbalance in antibiotic therapy because MRSA requires Gram-positive coverage not routinely given for community-acquired pneumonia. *P aeruginosa* pneumonia is traditionally covered with combination therapy consisting of an antipseudomonal β lactam and an aminoglycoside; the aminoglycoside has little other application and is somewhat toxic.

Recent data suggest that *P aeruginosa* might be overestimated as a pneumonia pathogen in intensive-care units.[14,19,20] A frequent coloniser of patients with chronic obstructive pulmonary disease, *P aeruginosa* might be regarded as a pathogen when isolated from respiratory secretions of patients presenting with pulmonary infiltrates, even if these infiltrates are secondary to congestive heart failure. The bitter irony is that antibiotic overprescription has led to the emergence of MRSA and multidrug-resistant *P aeruginosa*.

The 2005 guidelines[1] and proceedings of the Health-Care-Associated Pneumonia Summit[21] recommend initiation of empirical antibiotic selection by the explicit reporting of "health-care-associated pneumonia, ventilator-associated pneumonia, or health-care-associated pneumonia, suspected" (figure). Administration of empirical antibiotics on the basis of "suspicion of hospital-acquired pneumonia" is a pitfall that can readily lead to antibiotic misuse. The authors did recognise that such a strategy might lead to a situation in which antibiotics could be given for a non-infectious process and they encouraged de-escalation on the basis of serial clinical assessments

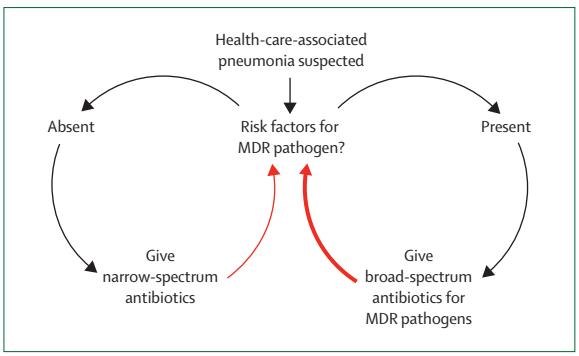

Figure: **The vicious circle within the hospital-acquired pneumonia and health-care-associated pneumonia guidelines[1]**
The key decision point is that of risk factors for multidrug-resistant pathogens, but the most important risk factor is previous administration of antibiotics (red arrows; thickness denotes relative risk). This classification can lead to widespread overuse of broad-spectrum antibiotics. MDR=multidrug-resistant.

and cultures. For example, the Clinical Pulmonary Infection Score criteria as applied by Singh and colleagues[17] identified patients who needed only 3 days of therapy (presumably because most did not really have pneumonia).

Advocates of empiricism emphasise that severe illness is an indicator of multidrug-resistant pathogens;[22] however, I suggest that severity of illness does not directly indicate microbial cause. When faced with patients who might die, many doctors feel the urge to cover every scenario no matter how unlikely. So, the notion that doctors are unwilling to miss anything has become a greater driving force for spiralling empiricism than has the likelihood that the pneumonia pathogen is *P aeruginosa* or MRSA. Because of the high mortality attributed to patients with hospital-acquired pneumonia who received inappropriate therapy, clinicians who cared for a population with high mortality needed to assure themselves that everything that could be done for critically ill patients would be done.

When I was an intern, antibiotics had become antipyretic agents—to be provided for fever of any unknown cause. This strategy was formalised for the neutropenic host and the floodgates opened. Any patient with an underlying comorbidity with a fever would be given an antibiotic. When I was a faculty member, antibiotics had become antihypotensive agents for the intensivist, and patients were given antibiotics if they "looked septic".

30–70% of patients with pulmonary infiltrates who receive antibiotics for suspected hospital-acquired pneumonia or ventilator-associated pneumonia do not have pneumonia.[18,23,24] Furthermore, this contagious behaviour of overprescription has infected doctors in emergency departments. The US Centers for Medicare and Medicaid Services mandate penalises emergency departments if antibacterial drugs for community-acquired pneumonia are not given within 6 h of admission.[25] As many as 50% of patients in some emergency rooms who receive empirical antibiotics for such infection will not have pneumonia.[26]

Proposed solutions

The heterogeneity of the population for which the 2005 guidelines[1] were intended and the elusiveness of a gold standard for establishment of microbial cause render them inherently unstable. The main objective of these guidelines was to ensure empirical antibiotic therapy would cover multidrug-resistant pathogens. Notably, the precipitating factor for emergence of multidrug-resistant pathogens including MRSA is prior antibiotic therapy, which propagates and aggravates the situation with unnecessary broad-spectrum antibiotic therapy. Two studies[15,17] that showed improved outcomes from pneumonia in intensive-care units reported that restriction of the common practice of broad-spectrum antibiotic was more important to improving outcomes than was use of the broader coverage sought by the guidelines committee. Monotherapy was effective in many patients with health-care-associated pneumonia who were ambulatory and not severely ill.[5,6] Therefore, the results in the study[7] by Kett and colleagues should perhaps not be surprising.

In an attempt to rectify the shortcomings of the guidelines, revisionists proposed to use the concept of risk factors for multidrug-resistant pathogens. Combination broad-spectrum therapy would be given to those patients with health-care-associated pneumonia and risk factors for multidrug-resistance and monotherapy would be given to the remaining patients with health-care-associated pneumonia.[21,22] This solution is exemplified by the vicious circle engendered by the 2005 guidelines (figure). Keep in mind that prior antibiotic therapy is the most important risk factor leading to multidrug-resistant pathogens.[2] Although the figure might seem to be an ironic exaggeration, it is not. It is figure 2 in the 2005 guidelines,[1] figure 6 in the proceedings[21] of the Health-Care-Associated Pneumonia Summit, and a variant of figure 1 in a review article on health-care-associated pneumonia.[22]

I believe the solution is straightforward—individualisation. If individualisation is applied to antibiotic selection, the regional differences in antibiotic use, unique characteristics of the population, and special situations can be taken into consideration. Every patient can be assessed with respect to their individual risk factors. The vulnerability of heterogeneity can be resolved by explicitly accepting that certain subgroups of patients have their own distinctive epidemiology and risk factors. For example, if a patient on haemodialysis is a known MRSA nasal carrier with a past history of MRSA infection or if *Legionella* spp are present in the drinking water of the hospital, such knowledge can improve antibiotic selection. Individualisation is useful when the patient's history is sufficiently complex that a one-size-fits-all approach is no longer feasible; this generalisation is the Achilles' heel of the health-care-associated pneumonia guidelines.[1] The guidelines expanded the population, so overprescription with broad-spectrum

antibiotic combination therapy was an imminent consequence. For example, provision of empirical MRSA coverage to a select population of drug addicts in Los Angeles, CA, USA who have a high prevalence of community-acquired MRSA would be rational, but blanket MRSA coverage might not be in Scandinavia, which has a low prevalence of such infections.

For an individualised approach, doctors require reasoning and a fund of knowledge. Administration of a single quinolone for community-acquired pneumonia was so much simpler; this widespread approach became the ultimate one-size-fits-all strategy. It was inexpensive and required neither contemplation nor cognition. Even microbiology tests for diagnosis became unnecessary.

I recommend guidelines be tailored to those specific settings that provide clues to the most likely pathogens: extended-care facilities and nursing homes (stratified by functional status), immunosuppressed hosts (stratified by patients with neutropenia, HIV status, or transplanted organ), and pneumonia in intensive-care units (stratified by ventilator-associated pneumonia and postoperative pneumonia). Patients receiving home intravenous therapy should not be included in the guidelines but their immunosuppressed status is pertinent.

A new development might assist with the solution. Molecular-based diagnostic tests are being introduced to the clinical setting at the point of care.[27–29] The emphasis on empirical therapy can be reduced if the microbial pathogens of pneumonia can be identified before antibiotic initiation. So, I suggest that a worthy effort of pneumonia investigators would be to apply, assess, and validate these new innovative diagnostic tests, including those for inflammatory biomarkers (especially procalcitonin).[30–32] A solution, if one exists, must focus on accurate identification of the pathogens of health-care-associated pneumonia.

The reflex pronouncement for more studies as a way of improving the 2005 guidelines is a safe recommendation, but not an easy solution. The 1996 and 2005 hospital-acquired pneumonia and health-care-associated pneumonia guidelines were formulated with the awareness that the basis for definitive pathogen identification for both infections was soft. It was thought that a consensus committee could somehow resolve this complex issue by a thorough review of the literature. This proved not to be the case. As Ewig and colleagues showed,[6] review of studies of health-care-associated pneumonia showed inconsistent and non-credible results, largely because of varying case definitions and inadequate bacteriology. Retrospective databases are unreliable for formulation of guidelines for antibiotic therapy. As an example, MRSA was the most common cause of community-acquired pneumonia (25%) and health-care-associated pneumonia followed by *S pneumoniae* (20·3%) in one such retrospective study[33]—a surprising finding that is unlikely to be replicated elsewhere.

Thus, the current literature cannot be used as an evidence-based foundation for guidelines on hospital-acquired pneumonia or health-care-associated pneumonia. One critique of the 2005 guidelines was aptly subtitled "eminence- rather than evidence-based".[34] For maximum effectiveness, new, large-scale, prospective studies on these infections need to be commissioned. Strict study design with objective endpoints is necessary. Standardised microbiological methods should be used, which must be applied to all patients. This flaw in previous studies was underscored by a study by Maruyama and colleagues,[35] which was the only recent study that detected atypical pathogens in health-care-associated pneumonia;[22,35] it was also the only study to test for such atypical pathogens. The net effect of selective testing of a pathogen rather than universal testing is underestimation for that particular pathogen in the population because the diagnostic test is not ordered, or overestimation of the virulence of the pathogen when tests are targeted for patients not responding to therapy or those who are severely ill. Such studies would also provide the opportunity to also assess molecular diagnostic tests and biomarkers.

A series of smaller studies with a well-defined population with health-care-associated pneumonia (eg, patients in a nursing home) is preferable to one large study with a heterogeneous study population. Because study populations in the numerous studies previously reviewed have been heterogeneous, the confidence intervals of the variables studied were inherently wide.

Obtaining appropriate evidence on which to base future guidelines is no small task, and federal funding sources will probably be needed. The investigators must be experienced; the CAPO[36] and CAPNETZ[30] study groups are candidates for leading such investigations. Much fruit would be borne if such studies could be done. And, if multiple studies were done, the foundation for evidence-based guidelines would be strengthened.

Conclusions

The 2005 ATS–IDSA guidelines lead to potential overtreatment. Because of the results of the study by Kett and colleagues,[7] doctors caring for patients in intensive-care should exercise restraint in antibiotic use. If point-of-care microbiological tests are not revealing, then monotherapy should be used for only 3 days in non-severely ill patients in intensive-care units as described in an algorithm published elsewhere[37] and then antibiotic therapy should be stopped when culture evidence suggests absence of infection. Because of the irremediable weakness of present data, the fundamental principles of infectious diseases need to be applied for hospital-acquired pneumonia and health-care-associated pneumonia until newer, more rigorous studies are done. Determine microbial aetiology and use empirical therapy only if necessary. A rational solution for effective management of pneumonia will ultimately rely on these principles.

Conflicts of interest

I declare that I have no conflicts of interest

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