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Perspective

Cost of nosocomial pneumonia: the example of vancomycin versus linezolid—shorter stay or fewer complications?

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SUMMARY

Hospital and national committees often focus on drug acquisition costs when taking decisions on the use of new drugs, but antimicrobial agent costs represent a minor part of the bill compared with the indirect costs of hospitalization or loss in days of productivity in working people. Although reducing the length of stay should be a main priority in the USA due to the indirect costs associated with hospitalization, adverse events, such as renal failure, have a major impact on healthcare resource use and costs. However, where hospital reimbursement is based on closed budgets, the paradox is that treating more patients due to reductions in length of stay may not be attractive to administrators, because the cost of discharging patients earlier is not compensated by the increase in severity in replacing stays of newer patient admissions. Furthermore, neuropsychological, physical, and immune impairment caused by sepsis has an extreme impact on long-term quality of patient life and health care resource consumption. Future research is warranted to further explore the potential impact of newer therapies for infections and sepsis, taking into account the costs of complications, effects on long-term quality of life, and particularly an international perspective, which requires customization for each national payer's system.

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Patients with infections caused by resistant bacteria have increased mortality, hospital length of stay (LOS), and healthcare costs. Results from the Extended Prevalence of Infection in the ICU (EPIC II) study suggest that the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant (MDR) Gram-negative organisms is higher in Asian than in American and European intensive care units (ICUs).¹ However, it appears that few studies have compared the economic outcomes associated with therapy in patients with nosocomial pneumonia (NP) from different geographical areas.

To address this gap, a study was recently performed to assess healthcare resource use (HCRU) and costs associated with MRSA NP from a Spanish payer's perspective.² The results showed that there were no significant differences in treatment costs between patients treated with linezolid (€17 782) and those treated with vancomycin (€17 423). The significantly higher drug cost for linezolid therapy compared to vancomycin therapy may have been partially offset by fewer renal failure events or shorter hospitalizations. Bed

costs were found to be the main cost driver, with ICU costs constituting the highest proportion; this is not the case in China.

Similar studies have evaluated the treatment costs of linezolid vs. vancomycin in patients with MRSA NP in the USA³ and China.⁴ When these studies were compared, it was unclear whether the conclusions from the USA study would remain robust when the Spanish or Chinese costs were applied, due to fundamental differences in each country's healthcare system. In Spain (and other European countries), healthcare is universally covered and fully funded from taxes obtained from the citizens. This means that health services are mostly free of charge at the point of delivery. In contrast, healthcare in the USA is not universally covered; there is no single payer for healthcare.

China also has a different healthcare system compared to most Western countries, adopting increasing health care privatization and decentralization from the central government to provincial and local authorities.⁵ Public hospitals in China are a critical part of the health system, accounting for 89% of total beds and 92% of hospital admissions. From the day of foundation of the Peoples' Republic of China to the early 1980s, local governments were responsible for the total financing of public health. In the late 1980s, reforms were introduced aimed at limiting government

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financial contributions into the health system (slowly reduced to as low as 7% of hospital revenues), and public hospitals were permitted to retain profits from sales of medicines (15% of total sales of medicines, becoming the main revenue source of public hospitals) and diagnostic examinations. However, the government continued to control the numbers of staff and beds, with very low fixed bed charges and medical and nursing services charges. Under this health policy, a huge increase in the costs of medicine and diagnostic tests was noticed during the last 20 years, but no increase in bed charges or medical labor costs. As the income from medical labor is low, the total number of doctors and nurses is much lower than required per bed in public hospitals. In 2009, another round of reforms was announced by the government aimed at increasing efficacy and reducing total costs. However, the goal needs further input from the government, as well as the reform of health insurance and payment systems. Since 2010,

medical services and pharmaceutical sales have been separated in some pilot hospitals, with more insurance reimbursements for adjusted medical services (not including bed charges).

Although the main conclusions of the European study are consistent with the economic analysis from the USA, there are some notable differences from the Spanish perspective.^{2,3} A key difference in the findings was that the total costs and cost components were lower from the Spanish payer's perspective compared to the USA (Table 1). This is consistent with the total medical expenditure data in Organization for Economic Cooperation and Development (OECD) countries: total medical expenditure in the USA was two to three-fold higher per capita than in most other OECD countries.⁶ Specifically, in 2014 the cost was estimated to be \$3053 (private) and \$2131 (public) per capita in Spain and \$9024 (private) and \$4448 (public) in the USA.⁶ This is also consistent with the findings of the ZEPHYR trial, in which it

Table 1
Health economic evaluation of MRSA nosocomial pneumonia: comparison of studies performed in the USA, China, and Spain (adapted from Rello et al.²)

	Niederman et al., 2014 ³	Wan et al., 2015 ⁴	Rello et al., 2016 ²
Country	USA	China	Spain
Healthcare system	Multiple payers (commercial and government payers coexist)	Decentralization from central government to provincial and local authorities	Government as the single payer (universal coverage)
Objectives	To compare the HCRU, costs of treatment, and cost-effectiveness of linezolid compared with vancomycin in the treatment of MRSA NP using ZEPHYR clinical trial data	To assess cost-effectiveness of linezolid vs. vancomycin in treating MRSA NP in China and the impact of renal failure on HCRU and costs	To assess the HCRU and costs for treating MRSA NP in hospitalized adults using linezolid or vancomycin, from a Spanish perspective; this study also evaluated the effect of renal failure on costs
Methods ^a	Costs were calculated by multiplying observed HCRU by unit costs for each type of use; unit costs were from a US payer's perspective and were obtained from the literature and First Data Bank (for drugs)	The cost analyses were performed for four selected large cities in China, which are economically and geographically diverse, representing the north, south, east, and west of the country; the unit costs were obtained from physician interviews (expert opinions)	Healthcare costs were calculated by multiplying observed HCRU (MV, bed-days by type, drug, and dialysis) by their own unit costs, respectively; the drug unit costs were obtained from Botplus-Portalfarma, and other medical service unit costs were obtained from the Oblikue database
Results ^b			
Comparing costs between treatments	No significant difference in the costs between patients treated with linezolid and vancomycin (\$45 004 vs. \$44 897, $p=0.96$)	No significant difference in the costs between patients treated with linezolid and vancomycin (Nanjing: ¥82 383 vs. ¥80 799, $p=0.70$)	No significant difference in the costs between patients treated with linezolid and vancomycin (€17 782 vs. €17 423, $p=0.51$)
Comparing costs between those who developed renal failure vs. those who did not	Patients who developed renal failure had a higher cost than those who did not (\$52 257 vs. \$44 176, $p=0.046$)	Patients who developed renal failure had a higher cost than those who did not (Nanjing: ¥100 449 vs. ¥74 944, $p=0.01$)	Patients who developed renal failure had a higher cost than those who did not (€19 626 vs. €17 388, $p=0.14$)
Cost-effectiveness ratio	\$16 516 ^d (95% CI -\$68 620 to \$164 478)	Nanjing: ¥15 904 (95% CI -¥161 935 to ¥314 987)	The cost-effectiveness ratio may be higher in the study from Spain than in the USA or China studies, since the incremental cost between treatments was the highest in Spain, although the incremental success rate remained the same across the three studies
Major findings	Patients treated with linezolid and vancomycin had similar overall costs Patients with renal failure had increased HCRU and costs	Linezolid was more cost-effective than vancomycin in treating MRSA NP from a Chinese payer's perspective Linezolid was associated with a significantly lower rate of renal failure than vancomycin	From a Spanish perspective, there were no statistically significant differences in total costs between the linezolid and vancomycin cohorts The drug cost of linezolid was partially offset by fewer renal failure events

MRSA, methicillin-resistant *Staphylococcus aureus*; HCRU, healthcare resource use; NP, nosocomial pneumonia; MV, mechanical ventilation; CI, confidence interval.

^a More details about the methods (including outcomes, statistical analyses, and cost-effectiveness techniques) and unit cost values can be found in the published USA and China studies.^{14,25}

^b The cost data in the USA (\$) and China (¥) studies were converted to equivalent cost in Euro (€). The cost data in the USA study were inflated to the same year (year 2012) as the Chinese and Spanish studies (Consumer Price Index for medical care items: <http://data.bls.gov/cgi-bin/survey/most>, accessed December 8, 2015) and then converted to equivalent Euro. The currency conversion rates (\$1 = €0.92, ¥1 = €0.14) were obtained from Google Finance (<https://www.google.com/finance/converter?a=1&from=EUR&to=USD>, accessed December 8, 2015).

Costs for linezolid vs. vancomycin converted to Euro: US €42,921 vs. €42,819, $p=0.96$; China €11,534 vs. €11,312, $p=0.70$; Spain €17 782 vs. €17 423, $p=0.51$. Costs for patients who developed renal failure vs. those who did not converted to Euro: US €49,838 vs. €42,131, $p=0.046$; China €14,063 vs. €10,492, $p=0.002$; Spain: €19,626 vs. €17,388, $p=0.14$. Cost-effectiveness ratio converted to Euro: US €15,751 (95% CI -€65,444 to €156,864); China €2227 (95% CI -€22,671 to €44,09).

^c The China study reported the cost data for four major cities in China; the city of Nanjing was selected for this table because the unit cost for Nanjing was in the middle among the four cities.

^d The median estimate of the cost-effectiveness ratio is provided.

was found that patients enrolled in European countries (10%) had an over 40% longer LOS than those in the USA (63%) (mean LOS 23 vs. 16 days), but lower total hospitalization costs for both treatment groups.⁷ The incremental difference in total cost between the linezolid and vancomycin groups was the highest in the European study² (€359), followed by that from China⁴ (¥1584 = €222)⁴ and that from the USA (\$107 = €102).³

Although some pharmaco-economic data regarding the selection of different antibiotics are available, most data come from the USA. Data on the economic burden associated with MRSA pneumonia in Europe are limited and vary widely across studies. Results from a Spanish study evaluating data from 27 hospitals found that MRSA bacteremia was associated with a mean inpatient LOS of 25 days, an ICU admission rate of 28.7%, and treatment costs of €11 884 per episode.⁸ A European study (EUVAP) concluded that patients who received inappropriate treatment had an ICU stay approximately 6 days longer than those who received appropriate empiric treatment.⁹ Decision-makers may use this information to justify the need for strategies aimed at the prevention of MDR and pneumonia, and clinicians may use this information to understand the economic burden associated with antibiotic treatment strategies.

Hospital and national committees often focus on drug acquisition costs when taking decisions on the use of new drugs, but antimicrobial agent costs represent a minor part of the bill compared with the indirect costs of hospitalization or loss in days of productivity in working people. (In an ongoing analysis of the economic costs of hospitalized community-acquired pneumonia, it was found that the cost of the antimicrobial agent was about 20% of the total cost; data not reported.) Of note, updated data on the economic burden associated with antibiotic treatment in patients with NP in the USA cannot be generalized. In particular, data derived from practice in the USA, where private practice reports double the costs of public practice,⁶ cannot be translated to countries with a national health service.

Although reducing the LOS should be a main priority in the USA due to the indirect costs associated with hospitalization, adverse events, such as renal failure, have a major impact on HCRU and costs. For example, in 2005, an increase in serum creatinine ≥ 0.5 mg/dl was associated with nearly \$7500 in excess hospital costs added to the bill.¹⁰ It should be emphasized that the high drug acquisition costs of newer antibiotics are partially offset by fewer complications, such as acute kidney injury events, which impact ICU, hospital bed, and renal replacement therapy costs. The potential consequences of developing renal failure include an increase in the odds of death, 4–5 extra days of hospitalization, and higher treatment costs.¹⁰ The renal failure rate in the ZEPHYR trial was significantly lower in the linezolid arm than in the vancomycin arm (4% vs. 15%, respectively; $p < 0.001$).⁷ Although not statistically significant due to the small cohort size ($n = 43$), the duration of mechanical ventilation was 6 extra days (13.3 ± 10.7 vs. 7.6 ± 3.6 days), the duration of the ICU stay was 5 extra days (14.4 ± 10.5 vs. 9.9 ± 6.6 days), and the duration of hospitalization was 3 extra days (19.5 ± 9.5 vs. 16.1 ± 11.0 days) for patients treated with vancomycin compared to those treated with linezolid. However, where hospital reimbursement is based on closed budgets, the paradox is that treating more patients due to reductions in LOS may not be attractive for administrators, because the cost of discharging patients earlier is not compensated by the increase in severity in

replacing stays of newer patient admissions. Furthermore, neuropsychological, physical, and immune impairment caused by sepsis has an extreme impact on long-term quality of patient life and health care resource consumption, which makes this a 'hidden public health disaster'.¹¹

Future research is warranted to further explore the potential impact of newer therapies for infections and sepsis, taking into account the costs of complications, effects on long-term quality of life, and particularly an international perspective, which requires customization for each national payer's system (http://ec.europa.eu/eurostat/statistics-explained/index.php/Healthcare_statistics).

Authors' contributions

JR contributed to the first draft; CB read it, edited it, and approved the final manuscript. Both authors made substantial contributions to the study, in data interpretation and manuscript preparation.

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