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Assessing antibiotic therapy effectiveness against the major bacterial pathogens in a hospital using an integrated index

Yong Chen‡, Boqiang Song‡, Xue Shan‡, Yanhong Qin§, Liang Wang¶, Hongyuan Wang¶, Zhongyi Lu', Lin Liu', Danping Yin§, Xuelin Han¶, Jingya Zhao¶, Shuguang Tian¶, Fangyan Chen¶, Xuetong Su', Liuyu Huang¶, Qi Li', Hajo Grundmann§, Hong Zhang** & Li Han*.

Aim: To assess the effectiveness of antibiotic therapy against five indicator bacteria in a Chinese hospital using an index-based approach. Methods: The study population comprises 1031 patients who had one clinically significant bacterial isolate in 2008, 2010 and 2013. Drug resistance index (DRI) based on pathogens was calculated. Results: The adaptive DRIs for Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus decreased, while both adaptive and fixed DRIs for Acinetobacter spp. increased from 2008 to 2013. The adaptive DRIs for Escherichia coli increased from 2008 to 2013, while the fixed DRIs exhibited a decreasing trend. Conclusion: DRI could be used to demonstrate the changes of antimicrobial resistance and prescribing over time as a result of evolutionary processes and governmental regulatory interference.

Antimicrobial resistance (AMR) is an increasing threat to the successful treatment of infectious diseases and has evolved to become a worldwide health threat [1]. Furthermore, because infections caused by resistant pathogens are associated with higher morbidity and mortality than those caused by susceptible pathogens, the impact of increasing resistance becomes a major concern [2,3]. It is believed that the evolving public health threat of AMR is driven by both appropriate and inappropriate use of anti-infective drugs for human and animal health and food production, together with inadequate measures to control the spread of infections [1,4].

There was an increasing level of AMR in China during the past decades, especially among those commonly identified nosocomial pathogens, including Acinetobacter baumannii, Staphylococcus aureus, Pseudomonas aeruginosa and Enterobacteriaceae [5]. Irrational use of antibiotics may have
contributed, as many Chinese hospitals rely on pharmaceutical sales for income, creating an incentive to overprescribe. One study estimated that a quarter of revenue in two hospitals came from antibiotic sales [6]. To combat AMR and reduce overuse of antibiotics, the National Health and Family Planning Commission of the People’s Republic of China (formerly the Chinese Ministry of Health) has adopted a series of measures to promote appropriate antimicrobial use since 2011 [7]. The effect of these measures on infection control and AMR is to be evaluated.

Clear information for policy makers about antibiotic resistance and its effect on public health has a crucial role in making this complex problem tangible, and simple indices such as the drug resistance index (DRI) might help to achieve this [8]. DRI is a newly developed method for aggregating bacterial resistance to multiple antibiotics and has been suggested as an intuitive measure to determine the average effectiveness of available anti-infective drugs in hospitals and primary care. One index, the adaptive DRI, is a measure of actual antibiotic effectiveness in different years, while another index, fixed DRI, allows for an assessment of the burden of AMR if antibiotic use patterns had not changed [8,9]. We also calculated another index, inadequate antibiotic treatment (IAT), which represents the fraction of patients for whom treatment does not provide adequate coverage and serves as a reference value for evaluating the effectiveness of antibiotic therapy [9,10] in this study.

This study aims to demonstrate the trends of antimicrobial use and drug resistance in a tertiary care hospital in three different years, and evaluated the effectiveness of anti-infective treatment through DRI analysis based on five indicator pathogens.

Methods

• Facility & study population

This study was conducted in a tertiary-care hospital with around 1000 beds in Beijing, China. The study patients comprised all inpatients at the hospital that were admitted in the year of 2008, 2010, 2013 (antimicrobial use strategy might have changed in these years due to governmental regulatory interference), and that had at least one bacterial isolate belonging to one of the five indicator pathogens (Acinetobacter spp., Escherichia coli, Klebsiella pneumoniae, P. aeruginosa, S. aureus). Pregnant women and residents of psychiatric facilities were excluded from the study. A case is defined as the first clinically significant isolate per patient and per hospitalization belonging to one of the five indicator species. This isolate should not come from a polymicrobial culture, should be associated with the receipt of antibiotic therapy and should be associated with one of the following special infection categories, including pneumonia or other lower respiratory tract infection, urinary tract infection, skin and soft tissue infection, bone and joint infection, bacterial peritonitis, bacterial meningitis, surgical site infection, blood stream infection and solid organ abscess.

• Data collection & management

Trained data collectors carried out laboratory data and patient chart-based review and entered results into an Epidata 3.1 database. Data for each index hospitalization were retrieved from medical records and microbiology lab results. All data used for analysis were de-identified in accordance to study protocol.

Patients were enrolled using a de-duplicated list of results sourced from the clinical laboratory database. Microbiological report of a positive index culture will be traced to a patient record for that (index) hospitalization. The data collected include: patient-level demographics, microbiological culture data (species, source, time of culture collection and susceptibility profile of the index culture that triggered the review), antibiotic treatment purposefully chosen on the basis of the laboratory susceptibility results (adjusted therapy) for the indicator infection associated with the index isolate. The susceptibility testing was conducted using the disk diffusion method according to the latest Clinical and Laboratory Standards Institute (CLSI) methodology, the results were interpreted according to CLSI criteria in each year [11–13].

• Statistical analysis

An adaptive DRI for each organism i was calculated according to methods described previously [8,9], using the formula:

$$\text{DRI}_i = \sum_k \rho_{ik} q_{ik}$$

where $\rho_{ik}$ is the proportion of resistance among organism i to antibiotic compound k and $q_{ik}$ is the relative prescribing of antibiotic compound k used to treat organism i in the same year of the
antibiotic susceptibility test. For contrast, a fixed DRI was calculated to measure the hypothetical DRI trend if proportional antimicrobial use remained unchanged since 2008. Differences between fixed and adaptive DRIs help quantify the contribution of adaptive prescribing, that is, to what extent actual treatment choices have changed in order to compensate for increasing AMR over time.

IAT was calculated in the following mathematical form:

\[ \text{IAT}_i = \frac{U_i}{N_i} \]

\( N_i \) is the number of patients who were diagnosed with pathogenic bacteria \( i \), and \( U_i \) is the number of patients who did not receive an effective antibiotic compound based on the antibiogram to organism \( i \). The 95% CI for adaptive DRIs and IATs were calculated using the bootstrap method as previously described [8,9]. The consistency between adaptive DRIs and IATs was analyzed by simple linear regression. Univariate analyses were conducted to evaluate the distribution of all variables. All statistical analyses were done with SAS version 9.4 (SAS Institute Inc., NC, USA).

- **Ethics statement**
  The study was approved by the institutional ethics committees of the Academy of Military Medical Sciences of the Chinese People’s Liberation Army, Beijing, China. As all data were anonymously collected and interpreted, the institutional ethics committees waived the need for written informed consent from the participants.

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**Results**

- **Distribution of indicator pathogens & infection types**
  In total, there were 1101 patients fulfilling our case definition in 3 years, among which 1031 patients (93.6%) received one of the 21 most common antibiotic regimens listed in Table 1 and were included in the calculation of DRI and IAT. Lower respiratory tract infection (\( n = 664 \)) was the most common infection type and was commonly associated with all the five indicator pathogens, while bloodstream infections and urinary tract infections were primarily caused by \( E. \) coli (Supplementary Table 1). 209 isolates of all the \( Acinetobacter \) spp. (90.9%) were identified as \( A. \ baumannii \).

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**Table 1. Antibiotic regimens: list of the 21 most frequently prescribed antibiotic regimens covered by the dataset, together with abbreviations used throughout this study.**

<table>
<thead>
<tr>
<th>Antibiotic regimen</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycoside</td>
<td>AMG</td>
</tr>
<tr>
<td>Aminoglycoside + cephalosporin (third generation)</td>
<td>AMG + CE3</td>
</tr>
<tr>
<td>Aminoglycoside + fluoroquinolone</td>
<td>AMG + FLQ</td>
</tr>
<tr>
<td>Aminoglycoside + piperacillintazobactam</td>
<td>AMG + PTZ</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>CAP</td>
</tr>
<tr>
<td>Carbapenems + fluoroquinolone</td>
<td>CAP + FLQ</td>
</tr>
<tr>
<td>Carbapenems + teicoplanin</td>
<td>CAP + TCO</td>
</tr>
<tr>
<td>Carbapenems + vancomycin</td>
<td>CAP + VAN</td>
</tr>
<tr>
<td>Cephalosporin (first generation)</td>
<td>CE1</td>
</tr>
<tr>
<td>Cephalosporin (second generation)</td>
<td>CE2</td>
</tr>
<tr>
<td>Cephalosporin (third generation)</td>
<td>CE3</td>
</tr>
<tr>
<td>Cephalosporin (third generation) + fluoroquinolone</td>
<td>CE3 + FLQ</td>
</tr>
<tr>
<td>Cephalosporin (fourth generation)</td>
<td>CE4</td>
</tr>
<tr>
<td>Cephalosporin (fourth generation) + fluoroquinolone</td>
<td>CE4 + FLQ</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>FLQ</td>
</tr>
<tr>
<td>Fluoroquinolone + piperacillintazobactam</td>
<td>FLQ + PTZ</td>
</tr>
<tr>
<td>Penicillins</td>
<td>PEN</td>
</tr>
<tr>
<td>Piperacillintazobactam</td>
<td>PTZ</td>
</tr>
<tr>
<td>Piperacillintazobactam + vancomycin</td>
<td>PTZ + VAN</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>TCO</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>VAN</td>
</tr>
</tbody>
</table>
Fractions of different antibiotic regimens & results of antimicrobial susceptibility

Figure 1A–E shows the estimates for the aggregated metrics used to calculate the DRI, which were obtained using the indicator bacteria dataset. The five figures show a longitudinal description of the adjusted prescribing practices and the results of antimicrobial susceptibility tests among patients in specified indicator bacteria group for each year. Each of the five figures represents one indicator species. An increase of resistance rates of carbapenem, aminoglycoside, cephalosporin (fourth generation) and piperacillin-tazobactam (PTZ) was observed in Acinetobacter spp. from 2008 to 2013, while carbapenem resistance was rarely identified in K. pneumoniae and E. coli in all 3 years. Carbapenem, piperacillin-tazobactam and fluoroquinolone were the most common antibiotics prescribed to treat bacterial infections.

Adaptive DRIs & IATs comparison

Values of the adaptive DRIs and IATs for each of the 15 scenarios determined by all the possible bacteria/year combinations are shown in Figure 2 and Supplementary Table 1. Simple linear regression of the 15 scenarios showed that the adaptive DRIs were highly related with IATs ($R^2 = 0.829$, $p = 0.034$). Under this circumstance, DRI can be interpreted as the proportion of isolates that the antimicrobial prescription did not cover.

Adaptive DRI trends in three different years

Figure 3 shows the changes of adaptive DRI values in 2008, 2010 and 2013. It is optimistic for K. pneumoniae, for which the DRI decreased from 0.22 in 2008 to 0.10 in 2010 and 2013, which means that only 10% of defined infections could not be treated with the prescribed regimens in years 2010 and 2013. A downward trend was also observed in P. aeruginosa and S. aureus from 2010 to 2013, although their DRIs were much higher than K. pneumoniae. Both Acinetobacter spp. and E. coli exhibit an increasing trend in DRIs from 2008 to 2013, with Acinetobacter spp. as the most refractory pathogens in 2013. It suggests that the proportion of Acinetobacter infections, which could not be treated with the available antibiotics, increased from 43% in 2008 to 58% in 2013 (Figure 3 & Supplementary Table 2).

Adaptive & fixed DRIs comparison

Figure 4 shows the adaptive and fixed DRI values among five indicator pathogens in 3 years. In general, the values of adaptive DRI were lower or similar to fixed DRI, except for E. coli, in which higher adaptive DRIs were observed, which might be related with restricted use of some antibiotics. Both adaptive and fixed DRIs in Acinetobacter spp. exhibit an increasing trend from 2008 to 2013, which reflects an increasing level of AMR for this bacteria.

Discussion

Reducing irrational use of antimicrobial agents is crucial for AMR containment [14]. Since 2011, formerly Chinese Ministry of Health has launched a special campaign to enhance the rational use of antimicrobials in healthcare settings. It mainly consists of establishing mandatory administrative strategies for the rational use of antimicrobials and setting targets for antimicrobial management [7]. ‘Administrative Regulations of Clinical Use of Antibiotics’ were issued in China in August 2012. Evidence showed that this campaign had notable achievements, with decreased antibiotic sales and a reduced percentage of prescriptions for antimicrobials for both hospitalized patients and outpatients [7,15–16]. When it comes to the defined infections caused by antimicrobial-resistant bacteria in this study, the physicians might face a difficult choice, as the use of some last line antibiotics was restricted. Our data revealed that the frequency of PTZ use has decreased in treating infections caused by all the five indicator bacteria after 2011 (Figure 1A–E), which indicated that prescribing was influenced by the administrative regulations, as PTZ was among one of the highly restricted antibiotics.

The overall decrease of antimicrobials use might had an impact on prevalence of AMR. A large surveillance program from China [17] showed that resistance of E. coli and K. pneumoniae to amikacin, ciprofloxacin and PTZ decreased from 2005 to 2014, and a marked decrease of methicillin resistance was also observed for S. aureus, while carbapenem resistance rates in A. baumannii in China are high. Although the overall trends of resistance patterns in this study are similar to previous studies, there are some exceptions. For example, the resistance rates of K. pneumoniae to carbapenems and cephalosporins were low in this study comparing to previous reports from China and other countries [17–19], this might be due to the strict selection criteria of study population, as only the first clinically significant isolate per patient and per
Figure 1. Distribution of prescription patterns and resistance patterns in five indicator bacterial pathogens from one hospital in 2008, 2010 and 2013. Figure 1A–E represents the results of *Acinetobacter* spp., *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, respectively. The left three panels in each figure show the relative frequency of patients treated with each of the 16 antibiotic regimens (17 antibiotic regimens for *S. aureus*); the right three panels show the fraction of isolates that were characterized as resistant to each of the 16 antibiotic regimens (17 antibiotic regimens for *S. aureus*).

AMG: Aminoglycoside; CAP: Carbapenems; CE1: Cephalosporin (first generation); CE2: Cephalosporin (second generation); CE3: Cephalosporin (third generation); CE4: Cephalosporin (fourth generation); FLQ: Fluoroquinolone; PEN: Penicillins; PTZ: Piperacilintazobactam; TCO: Teicoplanin; VAN: Vancomycin.
Figure 1. Distribution of prescription patterns and resistance patterns in five indicator bacterial pathogens from one hospital in 2008, 2010 and 2013 (cont.). Figure 1A–E represents the results of Acinetobacter spp., Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa and Staphylococcus aureus, respectively. The left three panels in each figure show the relative frequency of patients treated with each of the 16 antibiotic regimens (17 antibiotic regimens for S. aureus); the right three panels show the fraction of isolates that were characterized as resistant to each of the 16 antibiotic regimens (17 antibiotic regimens for S. aureus).

AMG: Aminoglycoside; CAP: Carbapenems; CE1: Cephalosporin (first generation); CE2: Cephalosporin (second generation); CE3: Cephalosporin (third generation); CE4: Cephalosporin (fourth generation); FLQ: Fluoroquinolone; PEN: Penicillins; PTZ: Piperacillin-tazobactam; TCO: Teicoplanin; VAN: Vancomycin.
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hospitalization were included in this study, the total number of isolates were low and might have some divergences comparing to the global resistance from surveillance studies. Another explanation is decreasing use of antibiotics in this hospital after 2011, especially for prophylactic use. However, it is difficult to assess trends of AMR burden without integrating data of AMR and antibiotics use, and communicating this problem to policymakers and nonexperts is complicated by the multiplicity of bacterial pathogens. That is why DRI was proposed previously [8] and employed in this study.

The analysis of DRI trends in five indicator-bacteria species showed that Acinetobacter spp. has become the most important drug-resistant bacteria in this hospital, with an increasing trend of both fixed and adaptive DRI values from 2008 to 2013. Increasing of fixed DRI suggested a rapid decay of antibiotic effectiveness for treatment of Acinetobacter infections in recent years. Increasing of adaptive DRI suggested that physicians did not have too many choices in case of drug-resistant Acinetobacter infection. Almost 60% of Acinetobacter infections could not be treated according to the adjusted prescribing choices, while Acinetobacter spp. accounted for around 22% of all the infection cases in this study. It was in accordance with previous studies which showed that Acinetobacter spp. has become one of the most important nosocomial pathogens in Chinese hospitals, especially in intensive care units [20,21]. Discovery of new antibiotics and enhancement of infection control measures targeted for Acinetobacter spp. are urgently needed.

The adaptive DRIs for E. coli increased while the fixed DRIs decreased from 2008 to 2013, which suggested in 2008 E. coli were more adequately treated than in 2013. It might be associated with restricted use of some antibiotics, primarily carbapenems. Comparing to fixed DRIs, the adaptive DRIs for K. pneumoniae, P. aeruginosa, S. aureus showed an obvious decline from year 2008 or 2010 to 2013, which suggested that physicians had more choices and could respond to the change of resistance patterns when treating infections caused by these pathogens.

Although the use of DRI in hospitals faces many challenges, including the difficulty of
Figure 3. Adaptive drug resistance indices calculated with data of prescription and resistance patterns of five indicator pathogens in 2008, 2010 and 2013. Shadow margins represent 95% confidence intervals derived using a bootstrap method with n = 1000 simulations. DRI: Drug resistance index.

This study has some limitations. First, this study was conducted in a single institution, and there is a clear predominance of *E. coli* over the other pathogens evaluated in urinary tract infections and blood stream infections, more studies on the use of DRI in analyzing the effectiveness of antibiotic therapy toward each single infection and bacterial species are needed in future. Second, the laboratory techniques have experienced some changes between 2008 and 2013 due to update of CLSI methodology, especially for the resistance breakpoints. It could have influenced the comparability of antimicrobial susceptibility results in different years. However, our results reflected the actual index values in each year. Third, the number of index cases was lower in 2008 than in 2010 and 2013, as this hospital experienced an expansions in these years, including increase of bed numbers, enlargement of patients’ sources and introduction of new equipment and techniques, which might have an impact on the accuracy of making comparisons. However, our study demonstrates not only the increase of AMR as a result of evolutionary processes through DRI analysis but more importantly changes in antibiotic resistance and prescribing over time,
which might be associated with governmental regulatory interference. These findings are very important for the audiences who are interested in the management of antibiotic resistance in low- and middle-income countries.

Although clinicians may not be familiar with this new index (DRI), its calculation methods and meanings are easy to understand. With the increasing availability of data on occurrence of AMR and fractions of antibiotic use, the applications of DRI in clinical field in future would become more extensive, which include: to determine the overall effectiveness of the current prescribing pattern (adaptive DRI) and the decay of antibiotic effectiveness over time (fixed DRI) in local hospitals; to assess the average effectiveness of antibiotic therapy for different categories of infections or bacterial pathogens, and further to identify high-risk population for intervention through correlating the DRI with actual disease burden; to evaluate the effectiveness of multidrug resistant organism (MDRO) control programs and restriction policy on antibiotic availability in hospitals; and to provide the evidence for revising the guidelines on infection control and antibiotic use in hospitals, and for requirement of invest in new drug development.

**Conclusion**
This study evaluated the effectiveness of antibiotic treatment through pathogens based DRI analysis in three different years in a Chinese hospital. It suggested that the increasing of antimicrobial resistance in *Acinetobacter* spp. might result from an evolutionary process, while for *Escherichia coli*, the antibiotic effectiveness has decreased possibly due to governmental regulatory interference.

**Future perspective**
The integrated index-based approach would be more extensively applied to track the effectiveness of antibiotic therapy in clinical field and aid in containing the increasing AMR problem worldwide.
Financial & competing interests disclosure
The study was supported by a grant from Beijing Natural Science Foundation (no. 7172157) and The National Special Project on Research and Development of Key Biosafety Technologies (2016YFC1200100) from the Ministry of Science and Technology, China. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research
The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Supplementary data
To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/fmb-2017-0025

SUMMARY POINTS
• Drug resistance index (DRI) is an integrated measure that combines the occurrence of antimicrobial resistance and fractions of antibiotic use in clinical practice.
• An increase rate of resistance to many commonly used antibiotics was observed in Acinetobacter spp. from 2008 to 2013, while carbapenem, piperacillin-tazobactam and fluoroquinolone were the most common antibiotics prescribed to treat bacterial infections in the hospital.
• The adaptive DRIs for the five pathogens in each year were highly related with another index (inadequate antibiotic treatment) based on coverage of antibiotic effectiveness.
• The adaptive DRIs for Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus decreased, while both adaptive and fixed DRIs for Acinetobacter spp. increased from 2008 to 2013.
• The adaptive DRIs for Escherichia coli increased from 2008 to 2013, while the fixed DRIs exhibited a decreasing trend.
• The index-based approach could be applied to evaluate the effectiveness of antibiotic therapy with the increasing availability of surveillance data on resistance and antibiotic use.

References
Papers of special note have been highlighted as:
• of interest; •• of considerable interest

•• A comprehensive study describing the epidemiology of antimicrobial resistance among the major clinical bacterial pathogens from China.


•• A comprehensive review describing the global situation of antibiotic resistance.


•• A comprehensive study describing the epidemiology of antimicrobial resistance among the major clinical bacterial pathogens from China.


• The first publication about the proposal of drug resistance index.


•• Suggested that the index-based framework can be an alternative approach to the estimation of point values and counterfactual trends in population-level empirical treatment appropriateness.


22 Evans RS. Electronic health records: then, now, and in the future. Yearb. Med. Inform. 25(Suppl. 1), S48–S61 (2016). Figure 1.