Introduction

The growing burden of antibiotic resistance and its association with antibiotic use highlights the need for the control and regulation of all aspects of antibiotic usage, including prescribing, dispensing and administration. A number of factors have been implicated in the development of antimicrobial resistance, with inappropriate prescribing being one of the most important.

Deuster, Roten and Muehlebach (2010) demonstrated that implementation of the treatment guidelines for the most commonly occurring infections in a tertiary care hospital in Switzerland resulted in an increase in the appropriate use of antibiotics. When devising the treatment guidelines for urinary tract infections and hospital-acquired pneumonia, the published guidelines, local sensitivity patterns and hospital antibiotic formulary were taken into consideration, and were therefore current and appropriate to the setting.

In the South African context, as part of the National Drug Policy, the government has made a commitment to ensuring the “availability and accessibility of medicines for all people”. The Essential Medicines List and the Standard Treatment Guidelines form part of the strategy to achieve the specific objectives of the National Drug Policy in the public health sector. The Essential Medicines List and Standard Treatment Guidelines are available for the primary care and hospital level management of patients. The hospital level guideline is available for adults and children. It outlines the management of conditions, including infectious diseases, under various categories, such as dermatological, nephrological and urological disorders. Specific chapters dedicated to ensuring rational antibiotic usage include systemic and nosocomial infections, as well as surgical antibiotic prophylaxis.

While the private sector is encouraged to adopt the guidelines, if applicable, anecdotal evidence shows that they are seldom, if ever, referred to in private hospital settings. The private sector remains largely unregulated in this regard, with formularies developed at some facilities at the discretion of hospital management. There is a paucity of information on the implementation of and adherence to these formularies.

It is imperative in a healthcare system in which both public and private sectors co-exist, that adequate steps are taken to ensure that both sectors contribute to rational antibiotic use in order to curb the growing threat
of antibiotic resistance which affects both the local and international context. While the public sector is guided by the Essential Medicines List and Standard Treatment Guidelines, guideline use appears to be suboptimal in the private sector. The factors which govern the selection of antimicrobial agents for infectious diseases in the private sector, where physicians and prescribers are largely independent, have yet to be defined and explored. Hence, there is a need for baseline surveillance of antibiotic prescriptions in the private sector in South Africa. Primarily, this would establish whether or not, and to what extent, the Essential Medicines List and Standard Treatment Guidelines or other guidelines are followed when managing patients who present with infection. This would ensure optimal outcomes, while limiting the emergence of resistant microorganisms in these facilities.1

Since antimicrobial agents are frequently prescribed to patients who are admitted to intensive care units (ICUs),2 the latter are an ideal setting with respect to the investigation of prescribing practices.

Method

Ethical considerations

Ethics approval was obtained from the Humanities and Social Sciences Research Ethics Committee of the University of KwaZulu-Natal, as well as the National Research Committee of the hospital group. Approval was also obtained from the hospital general manager of the private hospital in which the study was conducted. The collected information was anonymised, thus maintaining patient confidentiality.

Study design

A retrospective analysis of antibiotic prescriptions generated in three adult ICUs in a private hospital in KwaZulu-Natal was conducted over a two-month period, where the electronic profiles of patients were reviewed post discharge. These open ICUs included a surgical, medical and neurosurgical or post-cardiac surgery unit comprising 25, 26 and 8 beds, respectively. Patients who were prescribed antibiotics were included in the study and data were recorded as per the data collection tool shown in Table I.

Antibiotic prescriptions were evaluated against the clinical records to ascertain whether or not antibiotic therapy was indicated, and whether or not the choice, dosage and duration of the antibiotics were consistent with one or more of the guidelines stipulated within the Standard Treatment Guidelines and the Essential Medicines List for South Africa (2012 hospital level for adults),3 Infectious Diseases Society of America4-8 and the indications contained in the South African Medicines Formulary.4 Antiviral, antituberculosis, antifungal, prophylactic prescriptions and antibiotics used for off-label, non-antimicrobial indications, such as prokinetic use, were excluded, as were cases with missing or incomplete patient records. Patients presenting with Helicobacter pylori infection were also excluded from the analysis. In addition, patients presenting with evidence of established infection and antibiotic prescription prior to hospitalisation were excluded to provide an accurate picture of antibiotic use within the ICU setting alone.

Prescription analysis

Prescriptions were categorised as either treatment or prophylaxis, based on information, including theatre events, contained in the patient file, and prophylactic treatment was excluded from the study. Antibiotic treatment was then stratified according to the specialty, such as Orthopaedics, Nephrology and General Surgery, on the basis of the primary diagnosis undertaken by the primary physician or intensivist, and augmented by information contained in the patient records. In cases where an infection unrelated to or different from the primary diagnosis was present or suspected, this was categorised as a mixed infection, as was the case with patients making use of more than one specialty, as reflected in the primary diagnosis. Each prescription was assessed firstly in terms of whether or not antibiotic therapy was indicated on the basis of vital signs, inflammatory markers, laboratory tests and/or symptoms, and thereafter, one or several guidelines were applied, and therapy assessed in the context of choice, dosage and frequency.9-11 Duration was also measured for all prescriptions. If a microbiological evaluation was undertaken, the analysis included whether or not the choice of drug was consistent with the culture sensitivity result, and whether empiric therapy was de-escalated based on the culture result, if applicable. The preliminary categorisation and analysis conducted by a pharmacist were referred to a specialist microbiologist for confirmation. Consensus was achieved by a joint review of the patient records, where necessary.

Statistical analysis

SPSS® version 21 was used to analyse the data. A p-value < 0.05 was considered to be statistically significant at the 95% level of significance. Descriptive statistics, in the form of frequency (count) and percentage, were computed. Pearson’s chi-square was used for inferential statistics to determine whether or not the association between the variables was significant. The binomial test was used to determine whether or not a difference in the proportion of patients within a variable was significantly different.

Results

Eight hundred and twelve patients were admitted to the ICU over the two-month data collection period. Thirteen patients were still in progress at the time of discontinuation of the data collection and were thus excluded, as were 5 paediatric patients, resulting in a final total of 784 eligible patients. Of these, antibiotics were prescribed to 478 (61.0%) during their hospital stay. Patients on prophylactic antibiotics (n = 164) were excluded, and only those prescribed an antibiotic in the ICU for treatment purposes were included for further analysis. Following the application of additional exclusion criteria, the total number of patients to whom therapeutic antibiotics were prescribed in the ICU was 226 (28.8%). Two were excluded as the files were unavailable. Thus, the final sample for inclusion in the study was 224.

Table II provides a synopsis of the results, stratified according to specialty, in terms of whether or not antibiotic therapy was indicated, whether or not the correct dose of the antibiotic was administered at the correct frequency. Thus, Table II reflects an independent evaluation of the three separate parameters of antibiotic prescribing by the primary
Table 1: Data collection tool

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Site of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Patient allergies</td>
</tr>
<tr>
<td>Number of days in the ICU</td>
<td>Specimen source</td>
</tr>
<tr>
<td>Transfer ward</td>
<td>Wounds</td>
</tr>
<tr>
<td>Length of stay</td>
<td>Invasive procedures</td>
</tr>
<tr>
<td>Medical speciality</td>
<td>Discharged on antibiotics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug therapy</th>
<th>Microbiology cultures</th>
<th>Vitals</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date commenced</td>
<td>Date stopped</td>
<td>Antibiotic prescribed</td>
<td>Dose</td>
</tr>
</tbody>
</table>

CRP: C-reactive protein; ICU: intensive care unit; Temp: temperature; T/P: treatment/prophylaxis; PCT: procalcitonin; WBC: white blood cells
Adapted with permission from the Ampath clinical sepsis monitoring spreadsheet
physician or intensivist. A clear indication for antibiotic therapy was noted in 58.5% (n = 131) of patients, as shown in Table II, based on vital signs, inflammatory markers, laboratory tests and/or symptoms. 41.1% (n = 92) did not demonstrate any definitive signs of infection, and were thus deemed to have had no indication, while 0.4% (n = 1) remained unclear.

Table II: Summary of results per specialty

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Total</th>
<th>Indication</th>
<th>Microbiology</th>
<th>Correct dose and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Cardiology</td>
<td>42</td>
<td>9</td>
<td>42</td>
<td>9</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>9</td>
<td>3</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>General surgery</td>
<td>26</td>
<td>18</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>Mixed infection</td>
<td>72</td>
<td>58</td>
<td>62</td>
<td>27.7</td>
</tr>
<tr>
<td>Nephrology</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>4.5</td>
</tr>
<tr>
<td>Orthopaedics</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Pulmonology</td>
<td>38</td>
<td>30</td>
<td>33</td>
<td>14.7</td>
</tr>
<tr>
<td>Trauma</td>
<td>19</td>
<td>6</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Neurology</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Total</td>
<td>224</td>
<td>131</td>
<td>137</td>
<td>91.1</td>
</tr>
</tbody>
</table>

Microbiology, and dose and duration were positively and statistically significantly associated with indication using Pearson’s chi-square test (p < 0.05), attesting to the importance of microbiologically informed antibiotic therapy in terms of drug choice and a duration of 7-14 days or ≥ 14 days in terms of duration of therapy. Of all the patients in the sample (n = 224), microbiological tests were performed for 61.2% to guide antibiotic therapy. De-escalation was evident in only 13.1% of cases, while 8.0% of patients received the appropriate prescribed treatment according to the test results, and therefore could not be de-escalated any further.

The subset of patients with a clear indication for antibiotic therapy (n = 131) was further analysed in terms of choice, dose and frequency of therapy prescribed.

The percentage of patients for whom antibiotic therapy was prescribed during their ICU stay was 28.8%. This prescription rate is lower than that reported in previous studies, where rates as high as 73.4% were recorded, albeit inclusive of both prophylaxis and treatment.

When stratified, the binomial test indicated a significantly higher proportion of compliance at the 95% significance level (p-value < 0.05) in the Cardiology, General Surgery and Pulmonology patients, while the proportion of compliance with regard to mixed infections was significant at the 90% significance level. There was also a significant association with indication at the 95% significance level, with mixed infection patients showing the highest proportion of indication, followed by Pulmonology patients and those in General Surgery. A significant association was not found between drug choice, dose, microbiology and de-escalation.

Discussion

The percentage of patients for whom antibiotic therapy was prescribed during their ICU stay was 28.8%. This prescription rate is lower than that reported in previous studies, where rates as high as 73.4% were recorded, albeit inclusive of both prophylaxis and treatment. This may
be attributed to the well-established antibiotic stewardship programme currently in place at the facility where the stewardship committee meets regularly to provide updates on the hospital's antibiotic consumption data, thus ensuring that a level of awareness is consistently maintained. While engagement with prescribers in the private sector has traditionally been a challenge, pharmacists in the hospital are an integral part of the healthcare team. In addition to multidisciplinary ward rounds, pharmacist ward rounds ensure continued focus and a bedside review of individual patient prescriptions. However, antibiotic overuse and misuse is still evident, and more concerted effort is required by the antibiotic stewardship team.

Pharmacokinetic and pharmacodynamic parameters must be taken into consideration when prescribing and administering antibiotics to ensure that the concentration of drug achieved at the source of infection is sufficient to treat or eradicate infection. Understanding and applying these parameters contributes to the efficacious use of these agents. Dosing regimens should be designed based on the fundamental characteristics of individual antibiotics, particularly time-dependent versus concentration-dependent killing activity. Incorrect dosing and the excess use of antibiotics have also been identified as a driver for the development of resistance. Thus, the dose and frequency of administration are critical in ensuring optimal drug concentrations which ultimately contribute to effective therapy and the prevention or containment of resistance.

The percentage of patients prescribed correct doses was 91.1%, albeit not always indicated. Doses were deemed to be correct if the prescribed antibiotics were consistent with the drug registration information or currently accepted dosing regimens, while also taking into consideration patient risk factors, such as renal impairment. Non-compliance included incorrect dosing intervals, particularly for clarithromycin, cloxacillin, amoxicillin and clavulanic acid, co-trimoxazole, erythromycin, metronidazole and vancomycin. Incorrect doses were also noted for telithromycin, ciprofloxacin and vancomycin, and there were cases in which loading doses were not prescribed for teicoplanin, necessitating the implementation and awareness of the treatment guidelines.

Of the 58.5% of patients with a clear indication for antibiotic therapy, compliance with a guideline (national or international) or drug registration information was noted in 70.2% of patients. Drug choice was assessed for appropriateness and rational therapy. The combination drugs used were deemed to be appropriate if the combination was rational and pharmacologically justifiable. The choice of empiric therapy and combination therapy was a specific area of concern in this regard. Inappropriate combinations were evident in 69.2% of the 29.8% patients for whom there was a clear indication for antibiotic therapy, and included amoxicillin/clavulanic acid plus piperacillin/tazobactam, and meropenem plus imipenem.

Empiric antibiotic selection is based on a number of factors, including the site of suspected infection, likely causative organisms and local resistance patterns. Microbiology investigations, namely microscopy and culture, are essential in refining empiric therapy to the most appropriate and cost-effective, narrow-spectrum agent. In addition, de-escalation on the basis of microbiology results may limit the development of antimicrobial resistance. Timing with regard to the collection of the samples is also crucial in detecting infection by microbiological means as the causative organism may not be detected if empiric treatment has been commenced.

In terms of microbiological tests, 61.2% of patients underwent microbiological investigations to guide therapy. Of these patients, de-escalation was practised in only 13.1% of patients, while appropriate therapy was prescribed to 8.0%. 70.8% of therapy was not de-escalated, despite being warranted. The lack of de-escalation may be attributed to the reluctance of prescribers to make changes to critically ill patients' treatment regimens or the tendency to continue with therapy that appears to be effective. Nevertheless, this rate was concerning and represents a definite focus area for intervention with regard to prescribing practice.

The results also indicate that a greater percentage of patients with an indication for antibiotic therapy underwent microbiological tests compared to those with no definite indication. Therapy in the latter patients seemed to be pre-emptive, with prescribers exercising caution by covering for possible infection.

Prolonged duration of therapy has been identified as the largest contributor to the inappropriate use of antibiotics in wards and ICUs in hospitals. According to Havey, Fowler and Daneman (2011), a reduction in the treatment duration reduces usage and also limits adverse effects and selection pressure. Others have also noted that a shorter duration may be effective in preventing the development of resistance by reducing selective pressure on bacteria. While optimal duration of therapy should be individually determined, evidence exists to support a shorter duration. However, there are exceptions to this, and the decision with regard to optimal duration should be guided by clinical assessment and laboratory data.

The duration of antibiotic therapy measured in this study was purely descriptive, and included the complete duration of the patient's hospital stay. Antibiotics were administered to the majority of patients for 7-14 days, regardless of whether or not there was an indication.

**Conclusion**

While antibiotic prescription rates were relatively lower than those described in the international literature on antibiotic use in the ICU, antibiotic prescription in the absence of indication in 41.1% of patients, and the lack of microbiological verification in 38.8% of patients, together with inaccurate drug choice in 29.8% of the subset for whom antibiotics were indicated and incorrect dosing in 8.9% of patients, necessitate microbiologically informed therapy and compliance with the treatment guidelines. Inappropriate prescribing has frequently been addressed by practice guidelines aimed at improving antimicrobial utilisation.

Antibiotic stewardship is a key strategy in optimising treatment outcomes in individual patients, while limiting the emergence of resistance. Significant emphasis has been placed on these initiatives within the hospital group which served as the study site. While the impact was seen in some areas, such as appropriate dosing regimens, the opportunity exists for further improvement. Antibiotic stewardship should not only be

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**Original Research: An evaluation of antibiotic prescribing patterns in adult intensive care units**

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extended to include additional strategies, such as guideline development and implementation, but should also serve as the framework for best practice to ensure optimal patient care.

Declaration

Dipika Chunnilall is currently employed by the hospital group, and has received funding towards completion of a postgraduate qualification. The hospital group did not contribute to the study design, data collection methods, analysis and interpretation of the results, and writing of the manuscript.

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References