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**SASOCP position statement on the pharmacist’s role in antibiotic stewardship 2018**

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Antibiotics are the most commonly prescribed medicines in global healthcare practice today. Their effectiveness is crucial and often life-saving in humanity’s battle against pathogens and infectious diseases. Antibiotic/antimicrobial stewardship strategies and programmes have become vital to the preservation of effective antibiotics and the optimisation of their use. The South African Society of Clinical Pharmacy (SASOCP) has written this guideline to outline the importance, role and purpose of pharmacists in such stewardship programmes, both in the public, as well as the private hospital sectors in South Africa. It also provides an overview of various approaches to antibiotic preservation, behavioural change, stewardship measures, and monitoring strategies.

**Aim**

The South African Society of Clinical Pharmacy (SASOCP) has written this guideline to outline the importance, role and purpose of pharmacists in antibiotic stewardship programmes, in both public and private hospitals in South Africa.

Antibiotics are the most commonly prescribed medicines in both the community and hospital health care setting and are crucial, life-saving medicines in the fight against infectious diseases.1-4 Antibiotic utilisation world-wide has increased by 36% between 2000 and 2010, with countries such as China, India, and South Africa accounting for 76% of this increase.6,7 However, the increasing use of antibiotics, including their misuse, has escalated the prevalence of antimicrobial resistance (AMR).

This poses a devastatingly serious threat to public health as well as increasing costs.6,9 with the rise in AMR potentially resulting in AMR becoming a leading cause of death worldwide by 2050, reducing GDP by 2% to 3.5% and costing up to US$ 100 trillion per year.6,10 This requires urgent action across all countries and government sectors to reduce the imminent threat.6,7 Importantly, factors contributing to the rise of AMR include: incorrect selection of an appropriate agent, incorrect timing of administration, insufficient dosing and incorrect duration of therapy.11

The role of the antibiotic stewardship pharmacist includes the preservation of antibiotics through the monitoring, evaluation and guidance of appropriate antibiotic use. This includes review of the so-called 4 Ds of optimal antibiotic therapy: right **Drug**, right **Dose**, De-escalation to pathogen-directed therapy and the right **Duration** of treatment. This aligns to the aim of antibiotic stewardship (ABS), which, by definition, is “an ongoing effort to optimise antibiotic use in order to improve patient outcomes, ensure cost-effective therapy and reduce the adverse consequences of antibiotic usage, which includes antimicrobial resistance”.”12

1.1 **Antibiotic stewardship in South Africa (SA)**

Currently, novel antibiotic agents are in short supply and the need to conserve the remaining resources of effective antibiotics is of paramount importance.6 ABS refers to coordinated interventions designed to improve and monitor the appropriate use of antibiotics by promoting the selection of the optimal antibiotic agent(s), dose, duration of therapy, and route of administration. The goals of ABS can be separated into: optimising therapy for individual patients, preventing overuse and misuse of antibiotics and minimising the development of resistance at patient and community health levels. The last six years have seen major shifts in policy towards combatting antibiotic resistance within the SA healthcare environment. This culminated in the National Department of Health’s (NDoH) publication of SA’s Antimicrobial Resistance National Strategy Framework 2014–24 in October 2014, at a Ministerial Antimicrobial Resistance (AMR) Summit.13 One of the strategic objectives of the framework
was to ‘promote appropriate use of antimicrobials in human and animal health’ through ensuring access to safe, effective and affordable antimicrobials, institutionalising antimicrobial stewardship programmes across sectors, and addressing the use of antimicrobials in animal health and crop production. Parallel to this, and as part of the country’s drive towards quality healthcare service delivery, specific ABS and infection prevention control norms and standards were finalised and published for public comment in the Government Gazette, with a view of them becoming enforceable regulations. A need for ABS implementation and monitoring in SA was highlighted in a recent study where 47 private hospitals across SA revealed that close to one in every 15 prescriptions contained inappropriately prescribed antibiotics and required intervention. In addition, the study highlighted the significant role of SA pharmacists in antibiotic stewardship, since their collective efforts had a substantial impact on reducing antibiotic consumption in their respective hospitals. This demonstrates the influence that pharmacist-led stewardship programmes can have in settings where infectious disease-trained specialists are limited, and when integrated as part of the multi-disciplinary team (MDT).

Current research is being undertaken in public hospitals to assess the situation in this important sector.

1.2 Roles and responsibilities of the antibiotic stewardship programme members in South Africa

In the South African context, especially in the public sector, it is difficult to replicate resource-abundant stewardship models that are mostly driven by medical microbiology teams, infectious disease (ID) specialists and epidemiologists. Sustainable and effective antibiotic stewardship programmes (ASPs) largely depend on monitoring practices, teamwork in developing and implementing interventions, and organisational infrastructure. Consequently, it is critical in the SA context to utilise the existing resources of pharmacists, registered nurses (RNs) and other members of the healthcare team, who are well placed to coordinate anti-infective management and improve patient outcomes. For effective ASPs in SA, it is important to recognise the skills within Multidisciplinary team (MDT) that can support pharmacists to build effective ABS practices within the South African Antimicrobial Resistance National Strategy Framework and the associated Implementation Plan.

For ASPs to be successful, each member of the healthcare team should wholeheartedly execute the requirements of their role and responsibilities, resulting in an impactful stewardship programme. Figure 1 displays the potential key roles of the various players in a stewardship programme.

1.3 The role of the pharmacist in antibiotic stewardship

Of the 13 416 pharmacists registered in South Africa in 2015, around 37% are practicing in the public sector, a number which has steadily grown from around 16% since 2007. The average density of community pharmacies per head of population is around 0.61 per 10 000; however, with the inclusion of primary care clinics this nearly reaches the WHO benchmark of one clinic per 10 000 residents. Pharmacists can play a key role in the implementation of ASPs and although, to date, in SA this has not been a coordinated effort, recent evidence has shown success in the private sector.

The distribution of healthcare human resources remains inequitable across the private (well-resourced) and public sectors.
(poorly resourced) although several initiatives introduced by the government have been implemented to draw healthcare professionals into the public sector. Further to this, formal training for ABS has not been defined, nor mandated in SA, and currently the role the pharmacist can play in the ABS team would depend on the level of training that he/she has received. As custodians of medicine, pharmacists are well placed to lead and drive the antibiotic stewardship initiative, not only through audit and data collection, but also through relationship-building with prescribers to influence crucial prescribing decisions. The scope of a stewardship pharmacist, across the various sectors, includes:

- Driving and coordinating the hospital ASP
- Antibiotic prescription review
- Drug expertise
- Evaluation of the appropriateness of prescribed antibiotics for given indications
- Dose optimisation
- Duration optimisation
- Monitoring, interpretation and follow-up of microbiology results
- Development, education and maintenance of clinical guidelines
- Measurement and tracking of stewardship-initiated interventions
- Measurement and tracking of compliance to institution-specific guidelines
- Education and training of other healthcare providers
- Co-ordination of research on antibiotic stewardship

1.4 Antibiotic preservation strategies

Studies have shown that, rather than a single strategy in isolation, a combination of strategies described in this section, should be implemented, to have a sustainable impact on reducing the inappropriate use of antibiotics in hospital settings.

1.4.1 Formulary restrictions

The formulary was one of the earliest methods used to directly influence antibiotic utilisation, and contain costs when several therapeutic agents from the same class became available. Selecting antibiotics to include in a formulary requires the consideration of multiple factors, including: knowledge of local resistance patterns, avoiding agents with a similar spectrum of activity with no added benefits, drug costs and toxicity, amongst others. Formulary restriction protects agents that are more prone to resistance. Nevertheless, this strategy is rather broad and has not been proven to prevent overuse of available broad-spectrum antibiotics. However, this has depended on the acceptance and enforcement of formularies and treatment guidance. Consequently, we believe it is necessary to combine formularies with other strategies to optimise appropriate use of antibiotics in the future. This includes regular reviews of antibiotic use against current guidance and resistance patterns, as well as de-escalation strategies. Periodic reviews of the formulary are needed, depending on changes in resistance patterns, availability of newer agents, new knowledge of side-effects of the recommended antibiotics, and other significant factors.

Within the SA public sector, the implementation of the Essential Drugs Lists (EDLs) and Standard Treatment Guidelines (STGs) aids in the protection of antibiotics; however, this currently does not apply in the private sector.

1.4.2 Education and guidelines

Education is the most fundamental strategy by which prescribers may be influenced to adopt and maintain proficient prescribing practices and education forms a very important component of any ASP. Education can range from conference presentations, drug utilisation reviews and feedback, hospital pharmacy committee newsletters, student and provider teaching sessions, as well as the writing and dissemination of peer-reviewed clinical guidelines for certain infectious diseases. The implementation of guidelines has been shown to improve the probability of appropriate initial antibiotic therapy, use of narrower-spectrum antibiotic regimens, earlier intravenous (IV)-to-oral switch therapy, and shorter duration of therapies (DOTs) – without negatively impacting clinical outcomes. Of importance, however, is that guidelines need to be regularly reviewed and updated, and most importantly, combined with other educational efforts, as well as direct interventions and monitoring of compliance to enhance their implementation in an endeavour to improve future care.

1.4.3 Prior approval/authorisation of protected antibiotics

Prior approval/authorisation of protected antibiotics is another strategy that can be used to curtail antibiotic use, and requires justification for approval from the pharmacy or clinical head of the department for the use of certain antibiotics prior to prescription. This strategy has been identified as the most difficult to adhere to by prescribers, even though it can be the most effective in improving antibiotic prescribing. Approval can be obtained in many ways, including: telephonic authorisations, antibiotic order forms and direct interactions with prescribers. However, there can be concerns with formulary or antibiotic restrictions that need to be considered and addressed before implementation. These include: delays in initiating therapy, prescriber pushback, and unintended increases in the use of unrestricted antibiotics. To help preserve antibiotic sensitivity, prior authorisation of selected antibiotics combined with education of clinicians on criteria for use can ensure appropriate prescribing of antibiotics. For effective implementation of this strategy, support from the hospital administration, supply of the necessary resources with persistent efforts from committed and trained personnel, together with continuous communication between pharmacists and prescribers, will be needed.

1.4.4 De-escalation/streamlining

The persistent use of broad-spectrum antibiotics contributes to the increase in antibiotic-resistant pathogens. De-escalation/
streamlining is a method used to provide narrow-spectrum, targeted therapy following culture sensitivity results. The duration of antibiotic therapy can be reduced by shortening the course or terminating antibiotics if there is no evidence of infection. This is one of the most difficult strategies to implement and requires advanced training on the part of the pharmacist. The pharmacist must be aware of the full clinical picture of the patient, e.g. infection markers, response to treatment and other diagnostic measures before recommending such an intervention.

1.4.5 Prospective audit and feedback

Prospective audit and feedback (PAF) is an intervention that reviews antibiotic prescriptions and engages the provider after an antibiotic is prescribed. Improvements on antibiotic use, reduction in antibiotic resistance and decline in Clostridium difficile infections (CDI) have been seen in PAF interventions with no negative influence on patient outcomes. One study, conducted by a clinical pharmacist and infectious diseases (ID) physician, led to a 22% decline in the use of parenteral broad-spectrum antibiotics. In the ICU, PAF interventions showed a decrease in meropenem resistance and decreased CDI, without affecting mortality. The success of PAF is determined by the infrastructure and resources in place at an institution, as well as relationships and communication methods between pharmacists and prescribers. This process can be laborious and often requires ward bed-to-bed prescription surveillance. However, many interventions relating to PAF can be implemented at the point of dispensing in the pharmacy during evaluation and interpretation of the prescription chart. PAF improves antibiotic use and should be a fundamental component of any stewardship programme.

1.4.6 Pharmacokinetic and pharmacodynamic dosage optimisation

Pharmacology is based on two principles namely, pharmacokinetics (PK) and pharmacodynamics (PD). Conventional antibiotic dosing and administration should be optimised in accordance with PK/PD principles for clinical efficacy. Emerging data shows that PK/PD-based approaches to antibiotic prescribing should not only be used to improve clinical outcomes, but also to reduce AMR through favourable dosing as these principles ensure ideal dosing concentrations and the avoidance of ineffective sub-therapeutic antibiotic exposure.

In SA, PK/PD monitoring and adjustments should be implemented by hospitals for aminoglycosides and vancomycin due to inter-individual variation regarding PK/PD parameters. Contributing factors include the patient’s age, weight, gender, organ function and disease state. Sub-therapeutic antibiotic exposure is a contributing cause of mortality within the critically-ill patient population suffering from severe systemic infections, which further stresses the importance of dose-optimisation via PK/PD principles for antibiotics.

1.5 Behavioural change/modifications

Irrational prescribing is a global problem and interventions based on behavioural science may reduce this. There are many factors which can influence prescribing, which include cultural beliefs, socioeconomic factors, patient pressure, desire for clinical autonomy as well as “prescribing etiquette”; where prescribers are hesitant to alter prescriptions written by their colleagues. Prior to designing and implementing interventions to alter prescribing practices, it is important to conduct research regarding the factors which will influence prescribing practices in the specific institution. This will assist in determining what barriers will need to be addressed in order to successfully implement a particular intervention. Research has shown that senior colleagues and opinion leaders have more of an influence on prescribing practices than local policies and guidelines. Therefore, when designing interventions to change prescribing practice, it is imperative to involve senior clinicians and have their endorsement for any policy or guideline prior to implementation.

A study done by Burger et al in SA stated that the most important intervention to decrease antibiotic resistance rates, is education. Clinicians need to receive education on antibiotic prescribing guidelines and policies in their institution, as this will also lead to enhanced effectiveness of interventions. Meeker et al also found that socially motivated interventions, like accountable justification and peer comparison, significantly reduce irrational antibiotic prescribing. Such interventions resulted in a greater reduction of inappropriate prescribing, than education or observation alone.

1.6 Antibiotic stewardship measures

The following antibiotic stewardship measures (Table I) have been suggested by the South African Best Care Always (BCA) campaign and have been adopted by antibiotic stewards around the country.

1.6.1 Quantifying antibiotic stewardship outcomes

Currently there is no consensus with regards to which metric best quantifies antibiotic usage in hospitals. Metrics which may be used include Defined Daily Dose (DDD), Days of Therapy (DOT) and Length of Therapy (LOT). In ambulatory care, DDD and defined daily doses per 1 000 inhabitants per day (DIDs), (DIDs/1000 inhabitants/day) are typically used. In Point Prevalence Studies (PPS), antibiotic bed-days are also used.

1.6.1.1 DDD – Defined Daily Dose

The most commonly-used metric is DDD. DDDs are determined by the WHO (World Health Organisation) and represent the average daily dose of an antibiotic in an average patient. The DDD is calculated as the total number of grams of antibiotic agent used divided by the number of grams in an average daily dose. Consequently, DDDs can be used to measure antibiotic consumption and can serve as a measure to determine the impact of an ASP. Antibiotic usage in hospitals can be expressed as DDDs per 100 or 1 000 patient-days. The major advantage of
Table I. Antibiotic stewardship measures

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Measure</th>
<th>Pharmacist’s Level of Training</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empiric therapy without confirmation</td>
<td>Antibiotics prescribed without appropriate cultures</td>
<td>Pharmacist</td>
<td>Diagnostic microbiological cultures need to be taken before initiation of antibiotic therapy, to perform accurate ‘drug-bug matching’ and ensure the patient is on the most appropriate antibiotic for the infecting organism</td>
</tr>
<tr>
<td>Inappropriate choice of antibiotic agent</td>
<td>‘Drug-bug matching’</td>
<td>Pharmacist</td>
<td>Ensuring that each patient is on the correct antibiotic agent as per culture sensitivity results</td>
</tr>
<tr>
<td>Inappropriate combinations</td>
<td>Double Gram-negative cover, double Gram-positive cover, double antifungal cover, or double anaerobic agents</td>
<td>Pharmacist</td>
<td>Generally, more than one agent from each class should not be used simultaneously (i.e. two anti-Gram-positive agents, two antifungals; some antibiotic agents have anaerobic cover and the addition of metronidazole is considered double anaerobic cover; exceptions to this rule include double Gram-negative cover for certain Gram-negative infections, e.g. CRE)</td>
</tr>
<tr>
<td>Polypharmacy pertaining to antibiotics</td>
<td>The concurrent administration of four or more antibiotics</td>
<td>Pharmacist</td>
<td>The concurrent administration of &gt; 4 antibiotic agents is rarely considered appropriate. Duplication of spectrum of activity is a concern when a higher number of antibiotics are used concurrently and thus requires review.</td>
</tr>
<tr>
<td>Failure to de-escalate</td>
<td>Streamlining therapy from a broad-spectrum agent to a narrower-spectrum agent following culture sensitivity results</td>
<td>Advanced level training</td>
<td>Continuation of broad-spectrum therapy following evidence of sensitivity to a narrower spectrum agent can contribute to an increased risk of antibiotic resistance</td>
</tr>
<tr>
<td>Excessive duration of treatment</td>
<td>7–14 days</td>
<td>Pharmacist</td>
<td>Only in rare circumstances will treatment be necessary for &gt; 7 days, i.e. bone sepsis, endocarditis, known infections with MRSA, C. difficile, etc.</td>
</tr>
<tr>
<td>Inappropriate surgical prophylaxis</td>
<td>Correct agent at the correct dose, given at the correct time for the correct duration</td>
<td>Pharmacist</td>
<td>Improvement in compliance to appropriate antibiotic prophylaxis has been shown to decrease post-surgical site infections</td>
</tr>
<tr>
<td>IV-to-oral switch (IVOST)</td>
<td>Agents which are 100% bioavailable can be switched interchangeably Criteria for switching: Improvement in clinical status of patient Tolerate oral feeds Improvement of sepsis markers Oral formulation available</td>
<td>Pharmacist</td>
<td>They include: quinolones, voriconazole, linezolid, clindamycin, erythromycin, clarithromycin, metronidazole, fluconazole</td>
</tr>
<tr>
<td>Hang-time</td>
<td>Hang-time refers to the difference in time between the writing of the antibiotic prescription and the time it is first administered</td>
<td>Pharmacist</td>
<td>There is 7.6% mortality with every 1-hour delay in antibiotic administration for patients with sepsis and septic shock. Thus, hang-time should ideally not be longer than an hour in duration, for the first dose of antibiotics</td>
</tr>
</tbody>
</table>

[CRE: Carbapenem-Resistant Enterobacteriaceae]
would equal nine DOTs. Both DDDs and DOTs are useful for inter-
facility comparisons and facility-level monitoring of antibiotic
consumption.\textsuperscript{42} Important advantages of DOTs are that they
are unaffected by the dosage regimen the patient is receiving,
and they can facilitate a comparison between different classes of antibiotics
within the same institution. Conversely, a disadvantage is that
DOT may not give an accurate representation of antibiotics that
are administered multiple times on the same day.\textsuperscript{32,42,46}

1.6.1.3 LOT – Length of Therapy

Length of Therapy (LOT) represents the number of days a patient
receives antibiotic therapy. LOT does not take into consideration
the number of antibiotics the patient received. For example, if
a patient receives three different antibiotics for three days, it
would equal three LOTs. When compared to DOT, LOT gives a
more accurate estimation of the duration of antibiotic therapy.\textsuperscript{42}
An important activity for a stewardship programme involves
recommendations for LOT based on patient-specific factors.
Developing written guidelines with specific suggestions for
duration, including LOT recommendations as part of the
preauthorisation or prospective audit and feedback processes,
will experience the same pathogen prevalence and resistance
patterns. The pharmacist should play an active role in identifying
which antibiotics are most frequently used, and sometimes
overused, and can collaborate with microbiologists who can

provide input on hospital-specific pathogens and resistance
patterns.\textsuperscript{32}

1.7.2 Antibiograms

An antibiogram shows an overall profile of microorganism
susceptibility to a specific antibiotic in the hospital. Institutional
antibiograms will help to develop empiric antibiotic therapy
guidelines, which become vital whenever there are delays in
obtaining microbiology results.\textsuperscript{40} Stratified antibiograms include
parameters, such as patient location, population and infection
site, and can assist in optimising treatment recommendations
and guidelines. For example, certain resistant organisms may
be more prevalent in intensive care units (ICU) than in non-ICU
settings.\textsuperscript{32}

When constructing an antibiogram, it is important to control
the source of the isolates. For example, isolates from outpatient
samples should be excluded when constructing an antibiogram
in inpatients, and vice versa. Microbiologists should always be
consulted when trying to establish an antibiogram for a hospital,
because strict criteria and rules need to be applied to ensure
that the data reflected in the antibiogram is valid.

The Infectious Diseases Society of America (IDSA) supports the
use of stratified antibiograms over non-stratified antibiograms,
to assist in the development of relevant guidelines. Whilst

evidence that stratified antibiograms promotes improved
empiric antibiotic therapy is limited, stratification can reveal
important susceptibility differences.\textsuperscript{32}

1.7.3 Infection control

The transmission of highly-resistant bacteria from one patient
to the next, or from patients to healthcare workers and vice
versa, amplifies the problem of resistance. Figure 2 depicts the
strategic objectives, pertaining to infection prevention and
control, per the SA AMR framework strategy.\textsuperscript{13}

Figure 2. The strategic objectives, pertaining to infection prevention and control, per the SA AMR framework strategy.\textsuperscript{13}
They key to minimising such transmissions, is careful attention to infection control practices. Key elements of such practices, per the WHO, include:

- Appropriate barrier precautions for high risk patients (hand washing, wearing gloves and gowns)
- Appropriate isolation procedures depending on patient risk
- Adequate sterilisation and disinfection of supplies and equipment
- Use of aseptic techniques for medical and nursing procedures
- Training of healthcare personnel in appropriate sterile techniques and infection control procedures
- Maintaining appropriate disinfection and sanitary control of the hospital environment, including the air
- Provision of sufficient basins and hand/paper towels to regularly wash hands between patient contacts
- Recognition, investigation and management of outbreaks or clusters of infection
- Surveillance of hospital-acquired infections (HAI) and AMR
- Guideline development together with the standardisation of effective prevention practices and the implementation thereof (i.e. standard operation procedures)
- Assessment with feedback regarding IPC.

Pharmacist should adhere to the appropriate infection prevention and control protocols of the hospital whilst conducting bedside surveillance for ABS in the wards. This should include being ‘Bare Below the Elbows’ and adhering to hand hygiene practices between patients and whenever applicable.

Conclusion

AMR has become a very real and concerning threat to modern-day healthcare practice. The effective management thereof requires a decisive and multifaceted approach, which involves several members of the multidisciplinary healthcare team. The pharmacist is ideally positioned, and needs to play a central role within this setting, to facilitate and coordinate the implementation and monitoring of antimicrobial stewardship programmes (ASPs). Effective ASPs are required to preserve antibiotics via measures such as formulary restrictions, education and guidelines, pre-authorisations, de-escalation procedures, audits, and dose optimisation strategies. The successful implementation of such programmes will be greatly dependent upon the effective quantification and monitoring of stewardship outcomes.

References
