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PATHCHAT

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Antimicrobial stewardship (AMS) in the outpatient setting

Antimicrobial preservation, otherwise referred to as antimicrobial stewardship (AMS), does not only include limitation of inappropriate use, but also optimisation of antimicrobial selection, dosing, route and duration of therapy to maximise efficacy (clinical cure or prevention of infection), while limiting unintended consequences, such as the emergence of antimicrobial resistance (AMR), adverse drug events and cost.

Introduction

The majority of antibiotic prescriptions for systemic use are prescribed in the outpatient setting,[1] with acute respiratory tract infections (ARTIs) being the most common indication, followed by urinary tract infections (UTIs).[2] In fact, general practitioners (GPs) prescribe approximately 80% of all antibiotics, about half of which are unnecessary and are unlikely to benefit patients.[3] Inappropriate use of antibiotics for upper respiratory tract infections (URTIs), most of which are viral, significantly adds to the burden of antibiotic resistance.[4,5] The effect of these prescribing practices in ambulatory care on AMR can be observed at a patient level (up to 12 months)[6] and also at community practice level.[3] Despite these facts, many clinicians (and patients) do not see antibiotic resistance as a reason to refrain from inappropriate antibiotic use. The reasons driving the excessive prescription of antibiotics are complex and include constraints on clinician time, lack of appreciation of the impact on resistance, diagnostic uncertainty and perhaps – most importantly – patient and parental pressures. Hence, how clinicians implement AMS in ambulatory care is a challenging question. As such, the aim of this brief overview that focuses on antibiotic use as opposed to all antimicrobials is to propose a multi-component strategy-based approach to antimicrobial prescribing in the community.

A strategy-based approach to antimicrobial prescribing in the community

Strategies for optimising outcome while minimising the emergence of resistance in respiratory tract infections (RTIs) were previously reviewed.[7] These principles may be extrapolated and applied to antibiotic therapy for any infection.

Strategy 1. Treat bacterial infection only

Treating only bacterial RTIs should be self-evident, but is commonly ignored, probably because knowledge of how to distinguish clinically between non-bacterial and/or self-limiting infections, in addition to insensitive and non-specific infection markers, is lacking.

a. The use of C-reactive protein in primary care

The best-studied biomarker in community practices is C-reactive protein (CRP) testing for community-acquired pneumonia (CAP). Reviews have found that CRP has limited diagnostic value for pneumonia in primary care when the probability of pneumonia is below 10%.[8,9] Hence, the routine use of CRP in primary care is currently not recommended as it is unlikely to alter the probability of CAP sufficiently and the positive predictive value is too low to change subsequent management decisions significantly.[8,10] The same applies for routine CRP testing in URTIs such as patients presenting with a sore throat. Similarly, CRP alone is neither sufficiently sensitive nor specific to confirm exacerbations of chronic obstructive pulmonary disease (COPD).[11]

b. Optimise clinical diagnosis and severity assessment

Correct clinical diagnosis is obviously the key to reduce overall antibiotic prescribing. In fact, the recently published South African Antibiotic Stewardship Programme (SAASP) antibiotic prescribing guidelines contain concise algorithmic advice to guide prescribers based on clinical signs and symptoms, and summarises most of the common infections mentioned above (http://www.fidssa.co.za/images/SAASP_Antibiotic_Guidelines_2014.pdf).

c. Antibiotics for acute cough

Acute cough is one of the most common reasons for the prescription of antibiotics in ambulatory care as has been shown in Europe where 52.7% of adult patients presenting with an acute cough received one.[12] The median time for recovery is 11 days, during which time a patient frequently receives another unnecessary antibiotic despite the local inflammatory response that may persist for prolonged periods following a viral infection. Whaley et al.[13] recently demonstrated that of patients presenting in ambulatory care with an acute cough, the most common infective diagnoses were URTIs (46%), sinusitis (10%), acute bronchitis (9%) and pneumonia (8%). As the number of potential diagnoses increased from 1 to 2 and to ≥3, clinicians were more likely to express diagnostic uncertainty (5%, 25%, 40%, respectively; $p < 0.001$) and were consequently more likely to prescribe antibiotics (16%, 25%, 41%, respectively; $p < 0.001$).[13]

d. Need for tools to reduce diagnostic uncertainty
For these reasons, national guidelines should, if possible, focus rather on the provision of definitive "tools" (see Table 1) for clinical diagnosis in the outpatient setting rather than on the use of extensive additional diagnostic interventions. Guidelines should attempt to narrow the gap between recommendations and actual practice by acknowledging the diagnostic complexity and uncertainty faced by clinicians, particularly with regard to their ability to distinguish viral from bacterial infections.

Strategy 2. Judicious antibiotic prescribing principles

If a bacterial infection is determined to be likely and evidence suggests that antibiotics may provide benefit, several aspects of judicious prescribing should be considered.

a. Target maximum eradication of bacterial pathogens
Spontaneous recovery, which is the norm for mild-moderate bacterial RTIs, masks differences between the use of antibiotics or not, and allows sub-optimal agents or dosing to continue to be prescribed. This is referred to as the "Pollyanna" phenomenon, which applies where antibiotics with poor bacteriological activity appear to be as effective as those with superior or optimal bacteriological efficacy. Bacterial eradication is thus the primary goal of antibiotic therapy and should be the main determinant of therapeutic outcome.[7]

b. Utilise pharmacodynamics to choose the most effective agents and appropriate dosage
In order to achieve maximal bacterial eradication, clinicians need a basic understanding of the pharmacokinetic/pharmacodynamic (PK/PD) principles that govern how antibiotics exert their antibacterial action, as well the indices required for each class to achieve maximal efficacy.

c. Optimise duration of therapy
Several studies have shown that low dosage and/or long treatment duration increase the risk of carriage of resistant strains.[7] Five-day regimens of most antibiotics are clinically effective for uncomplicated acute otitis media (AOM) in children ≥ 2 years since eradication of organisms occurs within 72 hours.[4] A recent meta-analysis examined the efficacy and safety of short (3–7 days) vs longer courses (6–10 days) of antibiotic therapy for adults with acute bacterial rhino-sinusitis (ABRS).[4] No statistical difference in microbiological or clinical outcome was noted. Another meta-analysis similarly confirmed no difference in the risk of clinical failure, mortality, bacteriologic success, and adverse events between short-course (<7 days) and extended-course (>7 days) regimens for mild-moderate CAP.[14] In fact, several studies in children have demonstrated the equivalence of three versus five days of antibiotic treatment for CAP.[14] In summary, the benefits of shorter antibiotic courses are not only reflected in better patient compliance, but in fewer side effects, reduced costs and – most importantly – reduced risk of resistance. The "mantra" that should be communicated to clinicians is that where antibiotics are utilised in out-patients, a "high-dose short-course" strategy is preferred.

d. "Know your bugs"
It has never been as important for clinicians to "know their bugs". Not only does it appear that there are geographic differences between common RTI and UTI pathogens, but susceptibility patterns also differ (South African Society of Clinical Microbiology (SASCM). www.fidssa.co.za). It also appears that intra-city differences exist.

e. Minimise "collateral damage" – prescribing antibiotics that are associated with less selection of resistant strains
Collateral damage refers to the unintended consequences of an antibiotic regimen. Antibiotics differ between and within classes in their potential to select for resistance. Fluoroquinolones, the 2nd- and 3rd-generation cephalosporins and clindamycin are regarded as high-risk antibiotics, and restriction of these agents in Ireland, for example, has contributed to significant reductions in the incidence of *Clostridium difficile* infections (CDI), and extended-spectrum β-lactamase (ESBL)-producing bacteria and methicillin-resistant *Staphylococcus aureus* (MRSA) in both hospital and community settings.[15]

Similarly, in Finland, a significant association has been found between consumption of long-acting macrolides such as azithromycin and temporal and regional erythromycin resistance in *Streptococcus pyogenes*.[16] In South Africa, these agents are indiscriminately and frequently used in primary care for their anti-inflammatory and immune modulatory effects, but due to the confirmed long-term impact (up to 12 months in exposed patients) on AMR among common RTI pathogens and oral streptococci, their widespread use cannot be endorsed.[17] One aspect regarding collateral damage that is important to recognise is that although narrow-spectrum targeted therapy is preferable, inappropriate use of all antibiotics is the primary goal of an AMS programme.

Strategy 3. Vaccination as a key antimicrobial stewardship strategy

Vaccines are a key component in the fight against antibiotic resistance and a crucial component of a comprehensive AMS campaign.

a. Bacterial vaccines
- By targeting bacterial pathogens, vaccines directly reduce the need for antibiotics by providing direct protection from a bacterial disease
- Vaccines inhibit the carriage of bacteria targeted by the vaccine. Pneumococcal conjugate vaccines (PCV), for example, decrease the incidence of URTIs such as AOM and ABRS in children with an overall reduction in antibiotic prescriptions.[18]
- A further reduction in overall antibiotic consumption occurs due to indirect "herd" immunity. This relates to prevention/reduction in the transmission of pathogenic bacteria between unvaccinated members of the community.

The recent introduction of the PCVs (PVC7 followed by PCV13) in South Africa has had a profound and highly significant impact on drug-resistant, invasive pneumococcal disease (IPD) (see Figure 1). Von Gottberg et al.[19] recently demonstrated not only a dramatic reduction in penicillin (- 82%) and ceftriaxone-resistant (- 85%) pneumococcal infections, but also multidrug resistance (MDR) disease (- 84%).

A campaign to increase vaccine uptake should include a programme to promote AMS, both of which appears to be synergistic.

b. Viral vaccines
In addition to other antibacterial vaccines, such as diphtheria, pertussis and *H.influenzae* type B, vaccines against non-bacterial pathogens can also have a direct or indirect effect on antibiotic consumption by reducing:
- viral infections and fever syndromes where antibiotics are frequently inappropriately used; and
- complications of viral infections (e.g secondary bacterial infection) that require antibiotics.

In Finland,[20] 42% of children suffering from seasonal influenza receive antibiotics, but in a recent study by Kwong et al.[21] in Ontario, Canada, the increased use of influenza vaccination, following recommendations for universal vaccination in adults, resulted in a 64% decrease in anti-microbial prescriptions for influenza-associated respiratory disease. Targeting selected patient groups such as postpartum mothers is also beneficial. In Greece, influenza vaccination reduced acute respiratory illnesses, febrile episodes, influenza-like illnesses and health care visits in neonates born to vaccinated mothers by 37.7%, 50.3%, 53.5% and 41.8% respectively, and also reduced antibiotic prescriptions by 45.4%.[22] Similarly, Madhi et al.[23] recently found that influenzae vaccination provided protection in pregnant HIV-uninfected and HIV-infected South African women and that vaccination was also effective in HIV-unexposed infants up to six months after birth.

Table 1. Clinical parameters to exclude community-acquired pneumonia

Pneumonia is unlikely if the following are absent:
Fever ≥ 38 °C
Tachypnoea ≥ 24/min
Tachycardia ≥ 100/min
Evidence of consolidation on examination: crackles, bronchial breathing, fremitus
If any one of the above are present or coughing persists > 3 weeks
Then only perform a chest X-ray to exclude tuberculosis (of particular importance in South Africa) or lung cancer in smokers

Tabulated from Metlay JP, Kapoor WN, Fine MJ. *Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination*. JAMA 1997;278:1440-1445

Figure 1. Rates of disease caused by non-susceptible pneumococcal isolates by antimicrobial agent and year, South Africa, 2005–2012 among:

Figure 1A Children < 2 years

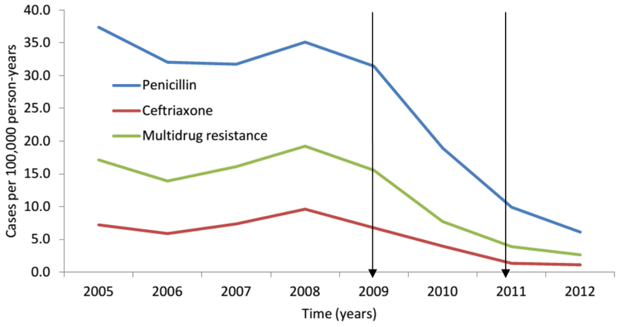
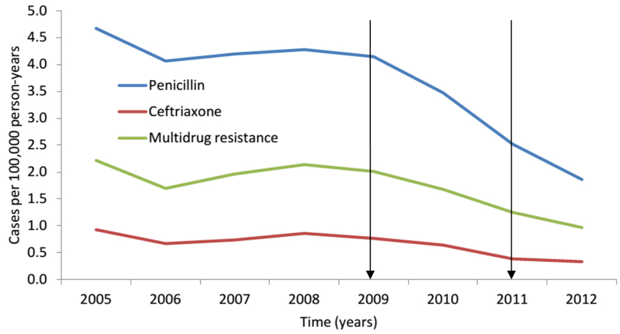


Figure 1B All ages



Reproduced and adapted with permission: The Massachusetts Medical Society. Von Gottberg A, de Gouveia L, Tempia S, et al. *Effects of vaccination on invasive pneumococcal disease in South Africa*. NEJM 2014;371:1889-1899.
PCV7 and PCV13 were introduced in 2009 and 2011, respectively.

Strategy 4. Immediate vs. delayed vs. no antibiotic prescription strategies

Accumulating evidence suggests that advice to delay the filling of an antibiotic prescription for uncomplicated RTIs, for at least the expected duration of the illness, is an effective strategy for reducing antibiotic use. In the largest study to date, Little et al.[24] combined structured advice regarding symptomatic therapy with no, immediate or delayed prescriptions, and confirmed that symptom control was no worse and that fewer than 40% of patients used antibiotics. In fact, there was little difference in antibiotic use between those advised to delay filling the prescription and those not given a prescription, because the former had been appropriately informed as to the lack of efficacy of antibiotics in this setting.

Despite progress in our understanding of the mechanisms by which prescriptions may be delayed for uncomplicated RTIs, the unique socio-economic circumstances in South Africa must be borne in mind. Most cases of viral and bacterial acute pharyngitis are self-limiting, including those caused by Group A beta-hemolytic streptococcal (GABHS) infections and as such the primary reason for considering antibiotic therapy in South Africa would be to prevent acute rheumatic fever (ARF).[4] AOM, however, is often viral in aetiology and even bacterial AOM frequently resolves spontaneously. As such antibiotics may be deferred for 48 hours while symptomatic therapy is administered. This approach is reasonable where good follow-up is possible in children ≥ 2 years of age.[4] Similarly, despite recent meta-analyses of antibiotics versus placebo showing only marginal or no benefit for ABRS[4], those patients from poor socio-economic environments should be given antibiotics at the first visit.

Strategy 5. Raise the "antibiotic threshold"

Reducing antibiotic prescriptions and consumption is in part, dependent on patient (or parental) involvement, and empowering the patient should be one strategy within a multi-faceted AMS approach aimed at primary care. Patient and parental beliefs, fears and expectations play a crucial role in determining whether or not a prescription will be provided. South Africans are no exception, as demonstrated in a study of KwaZulu-Natal GP practices, where Hofman et al.[25] proved that the factors most strongly associated with prescribing were the patient's opinion that antibiotics were required, his or her expectation of receiving them and the clinicians perception of this expectation.

Good communication between health care professionals and patients is therefore crucial and provision of appropriate evidence-based information on recognition of signs of severity and likely duration of illness can reduce anxiety (see Table 2). In order to raise the South African public's threshold before consulting a clinician (for self-limiting RTIs) to obtain an antibiotic script, the following is required: community awareness of AMR and patient empowerment. For example, patient information leaflets that describe the expected symptom duration and simple self-help measures significantly reduce antibiotic prescribing and re-consultations.[26]

Strategy 6. An "antibiotic license" to prescribe

A Cochrane review of interventions designed to improve antibiotic prescribing practice in ambulatory care[27] concluded that the use of printed educational material (such as this publication) or audit and feedback alone resulted in no or only small changes in prescribing practice. Patient-based interventions, particularly the use of delayed prescriptions, effectively reduced antibiotic use as discussed previously, but multifaceted interventions that combine clinician, patient and public education in a variety of creative ways were the most successful in reducing inappropriate prescribing.

The grave threat to the South African public of pan-drug resistance (PDR) among common community-acquired pathogens may warrant drastic measures, such as re-education of clinicians with regard to AMS. Several educational interventions are under consideration, including an "antibiotic license" for qualified, practicing South African clinicians. The proposed web-based course will allow prescribers to be registered with the Health Professions Council of South Africa (certification on completion of a learning portfolio) with the aim of equipping clinicians with the appropriate tools to understand, enhance and increase their acceptance of AMS strategies. While no detail can be provided at this stage, another long-term and different approach is required for medical students and postgraduates in training.

Strategy 7. Covering more territory to fight resistance in primary care

Of particular relevance to South Africa, the potential contribution of nurses in an outpatient setting could impact significantly on the rate of development of AMR. However, no specific data has been published defining the role of primary care nurses in clinics or in doctors' rooms. One randomised controlled study compared nurse vs GP care, and although the focus was not on antimicrobials, the surprising results suggested that the nurses would be most suitable for inclusion in a national AMS programme. Kinnersley et al.[28] found that patients who consulted nurse practitioners were generally more satisfied with their care, consultations were significantly longer and their patients reported being provided with more information. In addition, there were no notable differences for the other outcomes studied, including resolution of symptoms, allaying of concerns and prescribing. Nurses would therefore be ideally suited to decrease antibiotic consumption and potentially represent a time- and cost-efficient use of resources in a practice.

Similarly, little or no data exists for the role of community pharmacists. As patients frequently first pursue the self-medication route for colds or influenza-like illnesses, the pharmacist is also well placed to influence prescribing practice with symptomatic treatment and advice on the self-limiting nature of most ARTIs. They can also reinforce delayed prescriptions where applicable.

Strategy 8. Antimicrobial stewardship governance in primary care

Due to the diverse and unique settings in which health care is provided in the community (private practice GPs or specialists alone or in groups), clinicians, despite an awareness of AMR, mostly tend not to be accountable to anyone but themselves. While many of the core elements of hospital AMS programmes, such as leadership commitment (e.g. appointment of specific staff and ensuring that there is sufficient time to contribute to stewardship activities), accountability (e.g. identification of a single leader who will be responsible for programme outcomes) and support (e.g. organisational improvement) are relevant in the ambulatory setting, empowering such diverse clinicians to play a crucial role in AMS in the community and involving such prescribers in a sustainable way constitutes a particular challenge.

Gerber et al.[29], however, recently demonstrated that with relatively few resources relative to those of traditional hospital-based programmes, the automated use of generic data elements, which are increasingly common to all outpatient electronic health records, can be utilised in a most effective way to promote AMS. The intervention was performed in a large primary care (paediatric) network and consisted of clinician education plus personalised (tailored) audit and feedback of antibiotic prescription practices to patients with ARTIs. This resulted in a significant decrease in the prescription of broad-spectrum antibiotics to patients during acute primary care encounters. A clinician representative from each practice was specifically chosen to oversee the programme and ensure that AMS principles were followed. In fact, it does not have to be a clinician or infectious disease-trained clinician or pharmacist, as other health care and related workers are increasingly tasked with the responsibility of AMS. Skills beyond infectious diseases, such as understanding how to implement change and how to measure the success of a programme, are critical in the initiation and maintenance of an AMS programme.

Conclusion

To decrease AMR in the community, it is evident that similar to institutionalised AMS, multi-modal approaches are necessary. Reduction of antibiotic prescriptions, combined with the implementation of vaccination programmes, probably represents the most efficient strategy. In addition, assuming an antibiotic script is justified and appropriate, dispensing of less selective antibiotic compounds and the use of optimal dosage and duration is required. Prescribing antibiotics for patients with self-limiting conditions is counterproductive as it reinforces the belief that antibiotics are beneficial, and encourages repetitive prescriptions and consultations.

Communication with and education of patients is therefore the key. A long-term strategy of multidisciplinary, collaborative, educational programmes and interventions at many levels in society are required. For these reasons, clinicians, primary care nurses and pharmacists play a pivotal role in ensuring support for initiatives that seek to enhance patient empowerment and informed decision-making. However, the success would depend to a large degree on the barriers to change, not only among our clinicians and other primary health care providers, but also in our communities.

Table 2. Duration of respiratory tract infections

For all antibiotic prescribing strategies, patients should be given: • Advice about the usual natural history of the illness, including the average total length of the illness (before and after seeing the doctor):	
Infection	**Duration (days)**
Acute otitis media	4
Acute sore throat/acute pharyngitis/acute tonsillitis	7
Common cold	10–11
Acute rhinosinusitis	17–18
Acute cough/bronchitis	21
• Advice about managing symptoms, including fever (particularly analgesics and antipyretics)	

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