Auditing and Benchmarking of Azithromycin Utilization in Primary Care Military Clinics

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Despite widespread azithromycin use, no audit has targeted this drug to date. Azithromycin was audited in primary military clinics between July 1, 2003 and December 31, 2003 (period 1). Consumption (defined daily doses/1000 visits) and economic expenditure of penicillin V, amoxicillin, erythromycin, and azithromycin were evaluated. An educational intervention was performed (dissemination of local guideline regarding indications for azithromycin use) and its impact was assessed between July 1, 2004 and December 31, 2004 (period 2). During periods 1 and 2, 105 and 31 patients were prescribed azithromycin. Azithromycin was appropriately chosen in 5.7% vs. 70.9% of cases (p < 0.0001), but unnecessary in 90.5% vs. 16.2% (p < 0.0001). Azithromycin prescription during period 1 resulted in extrapolated excess expenditure of 420,000 New Israeli shekels/year (1 U.S. dollar = 4.5 New Israeli shekels). There was an attributable decrease of 52.1% in azithromycin consumption (adjusted attributable cost reduction 38.1%), but an increase in amoxicillin consumption (20.2%). Intervention decreased azithromycin consumption and expenditure but its effect was offset by increased consumption of other agents, mainly amoxicillin. Interventions in primary care settings should target prescribing behavior through a multifaceted approach to increase efficacy while preventing a trade-off effect.

Introduction

The emergence of antimicrobial resistance in the community setting and cost-containment efforts in medicine carry substantial implications on the treatment of community-acquired infections. Current regimens should not only be appropriate in terms of antibacterial spectrum, efficacy, and safety, but should be least expensive and least likely to promote antimicrobial resistance.

Azithromycin is an azalide that is active against streptococci, staphylococci, Haemophilus spp., Moraxella spp., Neisseria gonorrhoeae, Chlamydia spp., and Mycoplasma spp. Its broad spectrum, favorable safety profile, and convenience of use make it an attractive drug for treating community-acquired infections, especially acute respiratory infections (ARI). However, these advantages are offset by emergence of macrolide resistance and its higher cost. Therefore, auditing and benchmarking azithromycin use may be of great value.

Materials and Methods

Setting

This cross-sectional study was conducted in three primary care military clinics of the Israeli Defense Forces (IDF), located in basic training compounds across Israel. Of trainee and staff populations, >95% are ages 18 to 21 years and roughly two-thirds are men. Medical care at each base clinic is provided by four to six general physicians (GPs) 24 hours/day. GPs are a heterogeneous population comprised of local and foreign medical school graduates with varying experience, but none are board-certified specialists. GPs are either military medical officers or civilians employed by the military, representative of GPs stationed in other IDF clinics in terms of skills.

The oral antibiotic formulary in IDF clinics includes: penicillin V, amoxicillin, erythromycin, azithromycin, trimethoprim-sulfamethoxazole, nitrofurantoin, cloxacinil, and minocycline and is neither restricted nor audited. Azithromycin was added to the formulary 4 years before beginning of the study.

Data Collection

All IDF clinics utilize an electronic clinical patient record and, therefore, a complete database is available for all medical encounters and is suitable for surveillance of antibiotic use in primary health care. All variables were collected both at the clinic level as well as the entire IDF medical service level (when applicable).

We measured the total number of patient visits and visits due to diagnoses for which azithromycin may have been prescribed. Diagnoses (relating to the latter) were grouped according to IDF Medical Corps codes and included: sinusitis, upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), asthma, other respiratory disorders, ear disorders, and male genital disorders. Because International Classification of Diseases (9th Revision, Clinical Modification [ICD-9]) codes were not used during the study period, encounters pertaining to infection-related diagnosis groups may have also represented noninfectious disorders (e.g., visits for asthma not involving an acute exacerbation or visits for earache not caused by infectious
We identified all visits in which azithromycin was prescribed, records were retrieved and categorized per ICD-9. AAT was evaluated visit by visit by two investigators independently (U. Kopylov and J. Gilad). Interobserver variability was <5%. Discordant cases were reviewed by a third author (A. Borrer). The criteria used for AAT were based on antibiotic guides and official guidelines.7-14

AAT was assessed by allocation into one of four AAT categories: (1) complete agreement with all components of therapy—appropriate use; (2) agreement with chosen agent but therapy is pharmacologically inappropriate (dose, dosing interval, duration of therapy); (3) therapy indicated but chosen agent inappropriate (in relation to diagnosis, severity of illness, safety, cost); and (4) therapy is not indicated. The sum of AAT categories 1 and 2 represented a correct choice of azithromycin.

Study Design and Intervention Protocol

A preintervention audit was performed between July 1, 2003 and December 31, 2003 (period 1). Clinic GPs were unaware of the entire auditing process during this period to prevent a Hawthorne effect. Since substantial rates of inappropriate azithromycin prescription were detected during period 1, we devised a local guideline for benchmarking its use.

The following indications for azithromycin were allowed: (1) first-line therapy for acute nongonococcal urethritis in males; (2) acceptable first-line therapy for serologically proven pertussis; (3) acceptable first-line therapy for community acquired pneumonia; (4) first-line therapy for acute tonsillitis in penicillin allergic patients; (5) first-line therapy for acute sinusitis in pen-
Inappropriate azithromycin use at the clinic level during period 1 resulted in an excess of economic expenditure of 3,934 NIS. Assuming a similar rate of inappropriate therapy at the entire IDF level, the extrapolated excess economic expenditure on azithromycin in the IDF was calculated to be 420,000 NIS/year.

### Antimicrobial Consumption and Economic Expenditure

Antimicrobial consumption is presented in Table III. At the clinic level, there was a substantial decrease in azithromycin consumption but amoxicillin consumption increased by 45% and total consumption by 15%. When antimicrobial consumption at the clinic level was measured as number of courses per 100 visits at risk, a similar trend was found; azithromycin consumption decreased by 73% (3 vs. 0.8 courses/100 visits), that of erythromycin was unchanged, and that of penicillin V and amoxicillin increased by 5% (6 vs. 6.3 courses/100 visits) and 60% (5 vs. 8 courses/100 visits), respectively. Overall consumption increased by 4.5% between periods (15.3 vs. 16 courses/100 visits).

At the IDF level during the corresponding periods, there was an increase in azithromycin consumption by 11.1% and a marked increase in penicillin V and amoxicillin consumption, while erythromycin consumption decreased. Total consumption increased by 20.7% (attributable percent difference between clinic and IDF levels, -7.7%).

As shown in Table IV, economic expenditure on study agents decreased by 30% at the clinic level but increased by 2.2% at the IDF level (attributable percent difference, +32.2%). The adjusted economic expenditure decreased from 1,737 to 1,353 NIS/1,000 visits (percent change, -22.1%) at the clinic level but increased from 3,433 to 3,979 NIS/1,000 visits (percent change of +16%) at the IDF level. Therefore, the attributable effect of intervention on overall economic expenditure was a percent-change difference of −38.1%.

During period 1, azithromycin consumption at the clinics accounted for 41.6% of antimicrobial-related costs, but only 15.4% of costs during period 2, while at the IDF level, azithromycin consumption accounted for 43.4% and 41.8% of overall economic expenditure on study antimicrobials, respectively. Therefore, most of the decreased economic expenditure at the clinic level could be attributed to decreased azithromycin utilization.

### TABLE I

**OVERALL DISTRIBUTION OF INFECTION-RELATED DIAGNOSES PRE- AND POSTINTERVENTION**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Period 1 (%)</th>
<th>Period 2 (%)</th>
<th>P (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>URTI</td>
<td>74.3</td>
<td>69.7</td>
<td>&lt;0.0001 (0.8)</td>
</tr>
<tr>
<td>LRTI</td>
<td>3.1</td>
<td>3.2</td>
<td>0.67</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3</td>
<td>5.4</td>
<td>&lt;0.0001 (1.8)</td>
</tr>
<tr>
<td>Asthma</td>
<td>7.9</td>
<td>7.9</td>
<td>0.97</td>
</tr>
<tr>
<td>Other respiratory disorders</td>
<td>3.5</td>
<td>3.9</td>
<td>0.19</td>
</tr>
<tr>
<td>Ear disorders</td>
<td>3.8</td>
<td>4.2</td>
<td>0.21</td>
</tr>
<tr>
<td>Male genital disorders</td>
<td>4.4</td>
<td>5.5</td>
<td>0.0006 (1.27)</td>
</tr>
<tr>
<td>IDF level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>URTI</td>
<td>73.9</td>
<td>72</td>
<td>&lt;0.0001 (0.9)</td>
</tr>
<tr>
<td>LRTI</td>
<td>2.9</td>
<td>2.4</td>
<td>&lt;0.0001 (0.83)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>4.2</td>
<td>4.6</td>
<td>&lt;0.0001 (1.1)</td>
</tr>
<tr>
<td>Asthma</td>
<td>6.7</td>
<td>7.3</td>
<td>&lt;0.0001 (1.1)</td>
</tr>
<tr>
<td>Other respiratory disorders</td>
<td>4.3</td>
<td>5</td>
<td>&lt;0.0001 (1.17)</td>
</tr>
<tr>
<td>Ear disorders</td>
<td>4.2</td>
<td>4.3</td>
<td>0.23</td>
</tr>
<tr>
<td>Male genital disorders</td>
<td>3.8</td>
<td>4.4</td>
<td>&lt;0.0001 (1.15)</td>
</tr>
</tbody>
</table>

### TABLE II

**DISTRIBUTION OF INFECTIOUS DIAGNOSES AMONG PATIENTS PRESCRIBED AZITHROMYCIN PRE- AND POSTINTERVENTION**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Period 1, % (n = 105)</th>
<th>Period 2, % (n = 31)</th>
<th>P (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>URTI</td>
<td>21.9</td>
<td>0</td>
<td>0.004 (undefined)</td>
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<tr>
<td>Acute tonsillitis</td>
<td>1.9</td>
<td>19.3</td>
<td>0.0018 (12.3)</td>
</tr>
<tr>
<td>Acute sinusitis</td>
<td>7.6</td>
<td>19.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Acute asthma exacerbation</td>
<td>5.7</td>
<td>3.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>44.7</td>
<td>12.9</td>
<td>0.001 (0.18)</td>
</tr>
<tr>
<td>Community acquired pneumonia</td>
<td>0</td>
<td>22.6</td>
<td>&lt;0.0001 (undefined)</td>
</tr>
<tr>
<td>Acute otitis media</td>
<td>4.8</td>
<td>9.7</td>
<td>0.38</td>
</tr>
<tr>
<td>Nongonococcal urethritis</td>
<td>6.7</td>
<td>3.2</td>
<td>0.68</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4.8</td>
<td>3.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Other</td>
<td>2.9</td>
<td>6.4</td>
<td>0.32</td>
</tr>
</tbody>
</table>

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prescribed inappropriately, leading to suboptimal quality of care. We found that azithromycin has been commonly used in common infections such as ARI (85% and 87% in periods 1 and 2). Inappropriate prescribing was deemed appropriate (correct choice of drug) in 60.5% and unnecessary in 10.4%. Whereas our study did not have sufficient power to assess AAT by syndrome (only 136 cases treated with azithromycin in both periods), Jelinski et al.,24 have demonstrated that unnecessary therapy was significantly more common in ARI than non-ARI cases (17% vs. 0.9%). However, they did not address any particular agent.

Our study shows that azithromycin is commonly prescribed by military primary care physicians in Israel and that its consumption is twice that of erythromycin. Moreover, azithromycin consumption in the entire IDF has increased by 11% between 2003 and 2004, a similar trend to that observed in the IDF in the preceding 2 years (data not shown). This trend was coupled with an overall increased consumption of antimicrobials. Due to its higher cost, azithromycin comprised >40% of overall expenditure on studied agents and, therefore, benchmarking of azithromycin was expected to have the greatest effect on overall economic expenditure, according to the Pareto principle.

Surprisingly, studies dealing with antimicrobial consumption in the community have measured overall macrolide use without reference to new generation agents.22,23 This is also true for studies that evaluated consumption with the aim of correlating community antimicrobial use and emergence of resistance.3

Only one study measured azithromycin specifically, but unfortunately, azithromycin accounted for only 4% of prescriptions in the studied setting.20

Only a limited number of studies have specifically examined pharmacological aspects of AAT, demonstrating inappropriate rates of 30% to 90% in relation to dosage27 or duration of therapy.22 Only in our study, the rate of pharmacological inappropriateness of azithromycin was 7% in period 1 and 29% following intervention, despite that the recommended dose and duration were circulated to GPs. Bearing in mind that inappropriate dosing or dosing interval may lead to reduced cure rates or excess expenditure, the pharmacological aspects of antimicrobial therapy should receive more emphasis in future interventions.

We performed a limited educational intervention which successfully increased AAT and decreased unnecessary therapy, leading to a reduction of azithromycin consumption and related economic expenditure, despite its increased consumption in the entire IDF (attributable percent change of ~82%). Nonetheless, an increase of 15% in total antibiotic consumption occurred, which can be attributed to an increase in amoxicillin consumption. Therefore, although our intervention was highly successful in improving azithromycin use and reducing costs (adjusted attributable percent change of expenditure, ~38.1%), its effect on overall utilization was quite modest, and it can be speculated that GPs substituted amoxicillin for azithromycin instead of withholding unnecessary antimicrobial use when indicated.

Numerous intervention modalities have been used with the aim of improving antimicrobial prescription in the community setting with varying success, in part due to highly variable methodological quality. Single interventions that rely on

**Discussion**

This study evaluated AAT of azithromycin in military primary care. We found that azithromycin has been commonly prescribed inappropriately, leading to suboptimal quality of care and excess expenditure. Inappropriate prescribing was attributed to unnecessary therapy, inappropriaie choice of agents, and pharmacological inappropriateness.

The vast majority of patients treated with azithromycin in this study were those with ARI (85% and 87% in periods 1 and 2). This was not unexpected, given that ARI is the single most common infectious disease among outpatients and the most common infection for which antimicrobials are prescribed in the community.19 ARI (particularly URTI and bronchitis) are caused by viruses and are a leading cause of inappropriate antimicrobial use.16 Preintervention. URTI, and acute bronchitis comprised 66.6% of patients given azithromycin. Inappropriate prescribing for these conditions (up to 55% of cases) has been consistently demonstrated worldwide, leading to immense costs.17-23

AAT in our study was assessed by appropriateness categories, a method rarely used to date. We found an exceptionally high rate of unnecessary therapy in period 1 that significantly decreased following intervention. Jelinski et al.,24 have also categorized appropriateness, albeit differently; therapy was deemed appropriate (correct choice of drug) in 60.5% and unnecessary in 10.4%. Whereas our study did not have sufficient power to assess AAT by syndrome (only 136 cases treated with azithromycin in both periods), Jelinski et al.,24 have demonstrated that unnecessary therapy was significantly more common in ARI than non-ARI cases (17% vs. 0.9%). However, they did not address any particular agent.
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guideline formulation (such as in our study), physician education, or feedback reports have not necessarily been successful,30-34 mainly due to low acceptability by practitioners. On the other hand, multifaceted approaches are far more effective in changing behavior,5,35,36 as evidenced by randomized, controlled trials that have evaluated focus groups of GPs and/or patients,35,37 development of clinical guidelines in collaboration with GPs,35 production of education materials for patient and/or GPs,35,37-39 monitoring of prescribing behavior34 and feedback,38,39 and face-to-face physician instruction.38 Additional measures that have been used in the hospital are revision and restriction of the antibiotic formulary, development of clinical pathways, and real-time streamlining.40 Thus, current consensus favors the incorporation of behavior change models into educational interventions which should target not only the knowledge and attitudes of health care professionals but also that of the public.41-44

In conclusion, an educational intervention significantly decreased azithromycin consumption and overall economic expenditure in primary care military clinics. Interventions that focus on a selected antimicrobial agent may aid in achieving rapid restriction of use and substantial cost savings, but may adversely be associated with a trade-off effect. In light of the hierarchical nature of the military medical system, a focused educational intervention can be expected to be more efficacious than in civilian settings, but even in the military, suboptimal adherence of physicians to antimicrobial guidelines may occur. Future interventions should target physician prescribing behavior through a multifaceted approach to influence the culture of antibiotic prescribing.

References


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