PharmaNote®

Volume 17, Issues 8–9 June/July 2002

Protopic®:
An Alternative to Topical Steroids in the Treatment of Atopic Dermatitis

Thomas J. Murray III, Pharm. D. Candidate

Introduction

Atopic dermatitis (eczema) is a commonly found skin disorder present all over the world. It is a chronic inflammatory skin disease affecting 5-10% of the population in the U.S. (about 15 million people). The disease has both genetics and susceptibility to environmental irritants as predisposing factors. Individuals affected have intense itching, xerosis, erythematic lesions, rash, exudative erosions and increased vulnerability to cutaneous infections.[1,2] Typically the only treatments have been topical steroids, oral antihistamines and antibiotics when infection is present. Protopic® (topical tacrolimus) is a new drug designed to combat atopic dermatitis.

Protopic®, manufactured by Fujisawa, is the first new drug to treat atopic dermatitis in 40 years. It was approved by the FDA in December of 2000 and is indicated for short-term and intermittent long-term therapy in the treatment of patients with moderate to severe atopic dermatitis in whom the use of alternative, conventional therapies are deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies.[3] This article will address the pharmacology, clinical trials, dosing, adverse effects and costs of Protopic® therapy.

Pharmacology/Pharmacokinetics

Tacrolimus is the first in a new generation of topical immunomodulators (TIMs)[3]. When applied topically tacrolimus complexes with protein FKBP-12, found in T-cells. This complex eventually binds calcineurin and blocks the transcription of cytokines thus inhibiting further T-cell activation and a proliferation of the immune response.[2,3] Tacrolimus may also act by binding to cell surface steroid receptors, inhibiting the release of mast cell mediators, downregulate IL-8 receptors and decrease intracellular adhesion molecule-1 and E-selectin lesional blood vessel expression. All of this leads to decreased recognition of antigen and a general decrease in the entire inflammatory cascade.[2]

The kinetic profile of this drug is essentially non-existent. It is a topical ointment that does not reach systemic circulation to any clinically significant degree. The average peak blood concentrations of tacrolimus are <1 to 5 ng/mL which are less than the trough concentrations of 5-20 ng/mL seen in patients on tacrolimus therapy to prevent organ rejection.[2,4]

Clinical Trials

Tacrolimus was used as monotherapy to treat atopic dermatitis in two identical randomized, double-blind, comparative studies. A total of 632 adults (age >15 y/o) were treated for up to 12 weeks or until 1 week after complete resolution of symptoms. Efficacy was determined by the physician's global evaluation of clinical response at the end of the study period. The results of the study showed that both concentrations of tacrolimus ointment were indeed superior to vehicle alone in treatment of atopic dermatitis. In this study, African American patients benefited more from the 0.1% ointment versus the 0.03%, most likely due to a

lower percutaneous penetration/absorption of topically applied agents compared with Caucasian patients. A more compact stratum corneum and higher epidural lipid content are thought to explain these racial differences. No other variations in patient population seemed to affect the outcome of therapy. Treatment with tacrolimus 0.1% and 0.03% lead to statistically significant healing rates compared to vehicle alone (see *Table 1*).[5]

In a second study, 351 children (2-15 y/o) were followed in a randomized, double-blind, parallel group, 3-arm, intention to treat, vehicle-controlled study where tacrolimus was used as monotherapy. Patients were again treated for up to 12 weeks or for 1 week after complete resolution of symptoms. Even though the evaluation criteria (improvement of 90%) were stringent, over one-third of tacrolimus treated patients saw this level of improvement while the majority of the vehicle ointment group had no appreciable improvement or were worse off at the end of the study. This study noted no appreciable difference between varying patient demographics and effective tacrolimus treatment. Overall there was a statistically significant higher healing rate with tacrolimus over vehicle alone (see *Table 2*).[6]

Table 1. Adult Response[5]

Physician's Global Evaluation of Clinical Response (% Improvement)	Vehicle Ointment (N = 212)	Protopic® Ointment 0.03% (N = 211)	Protopic® Ointment 0.1% (N = 209)
100%	2 (1%)	21 (10%)	20 (10%)
≥90%	14 (7%)	58 (28%)	77 (37%)
≥75%	30 (14%)	97 (46%)	117 (56%)
≥50%	42 (20%)	130 (62%)	152 (73%)

Another study looked at the efficacy and safety of tacrolimus treatment on refractory facial lesions in atopic dermatitis following topical steroid discontinuation. This study included 47 patients (ages 18-63 y/o) with refractory facial atopic dermatitis, of whom 38 had used topical steroids for at least 4 weeks before enrollment (Group 1) and 9 that had not received steroid treatment (Group 2). All patients received 0.1% tacrolimus ointment and the severity index and pruritus scores were assessed as an atopic dermatitis activity index each week and compared with baseline data. The data showed that both groups showed excellent improvement and Group 1 showed no evidence of a rebound phenomenon commonly seen when steroids are discontinued in patients with atopic dermatitis. There were no serious systemic adverse effects noted in this study and mild burning at the site of application was the major topical adverse effect noted, present in 66% of the study population (although only transient and not occurring past the third day of treatment on average).[7]

Dosing

Tacrolimus is available in 30g and 60g tubes of two strengths, 0.03% and 0.1%. The 0.03% strength is indicated for the treatment of atopic dermatitis in children ages 2-15 years. It is applied as a thin film twice daily with treatment continuing one week past the resolution of symptoms. The 0.1% strength is indicated for those over 15 years of age. It is also applied as a thin film twice daily with treatment continuing one week past the resolution of symptoms, this may take about three weeks.[2,3] Also, occlusive dressings should not be used as this can lead to increased systemic availability of the drug and subsequent unwanted side effects.

Table 2. Pediatric Response[6]

Physician's Global Evaluation of Clinical Response (% Improvement)	Age 2-15 y/o	
	Vehicle Ointment (N = 116)	Protopic® Ointment 0.03% (N = 117)
100%	4 (3%)	14 (12%)
≥90%	8 (7%)	42 (36%)
≥75%	18 (16%)	65 (56%)
≥50%	31 (27%)	85 (73%)

Adverse Effects

In numerous clinical trials the most commonly reported adverse effects were a sensation of burning upon use of tacrolimus, pruritus, flu-like symptoms, skin erythema and headache. Two randomized, double-blind, comparative, vehicle controlled studies involving 631 adults with moderate to severe atopic dermatitis showed that the previ-

Table 3. Incidence of Adverse Effects with Protopic® [8]

	Treatment Group			p-value	
	Vehicle (n = 212)	0.03% (n = 210)	0.1% (n = 209)	0.03% vs. vehicle	0.1% vs. vehicle
Skin burning	25.8 ± 3.43	45.6 ± 3.50	57.7 ± 3.52	<.001	<.001
Pruritus	36.5 ± 3.70	46.1 ± 3.57	46.1 ± 3.59	.059	.062
Flu-like symptoms	19.3 ± 4.06	23.2 ± 3.28	30.8 ± 3.61	.451	.034
Skin erythema	19.8 ± 3.04	24.8 ± 3.07	27.9 ± 3.19	.250	.066
Headache	10.7 ± 2.79	20.0 ± 2.99	19.2 ± 2.99	.022	.036
Skin infection	10.6 ± 2.67	12.4 ± 2.50	4.7 ± 1.65	.617	.063
Skin Tingling	2.4 ± 1.04	3.4± 1.27	7.6 ± 1.91	.522	.015
Acne	1.8 ± 1.30	4.3± 1.48	7.1 ± 2.02	.213	.028

ously mentioned AE's had a significantly higher incidence in the tacrolimus treatment groups versus the vehicle group (see *Table 3*).[8] Although these AE's were more severe in the tacrolimus groups, there was a higher rate of completed treatment in these groups compared to the vehicle groups (see *Table 4*).

An open-label, long-term, non-comparative safety study enrolled 255 children (ages 2-15 y/o) to assess early discontinuation of therapy in pediatric populations (see *Table 5*)[9]. The patients were evaluated at baseline, 1 week, and 3, 6, 9, 12 months and 1 week after each time remission was achieved. Again the major AE noted was burning and pruritus at the site of application and typically lasted less than 10 minutes and 1 hour respectively. Although not specifically assessed there were no reports of skin atrophy or growth retardation.

Table 4. Adult Discontinuation[8]

	Vehicle	0.03% Tacrolimus	0.1% Tacrolimus
Number of Patients	212	210	209
Completed Treatment	67 (31.6)	149 (71.0)	157 (75.1)
Prematurely Discontinued Treatment	145 (68.4)	61 (29.0)	52 (24.9)
Adverse Event	26 (12.3)	13 (6.2)	11 (5.2)
Lack of Efficacy	95 (44.8)	26 (12.3)	18 (8.6)
Administrative	24 (11.3)	22 (10.4)	23 (11.0)
No. Treatment Days mean (median)	40.0 (22)	69.4 (84)	68.1 (84)

Cost of Therapy

The price of a 30 day supply of Protopic® varies between amount used and strength used. A summary of average retail pharmacy prices can be found in *Table 6.*

Table 5. Pediatric Discontinuation[9]

	No. Patients (%)
Enrolled	255
Prematurely Discontinued	66 (25.9)
Lack of Efficacy	8 (3.1)
Administrative Reason*	48 (18.8)
Any Adverse Event	10 (3.9)
Application site irritation	5 (2.0)
Non-application site irritation	5 (2.0)

* Administrative reasons include lost to follow-up, non-compliance, patient refusal, etc.

Summary

Targeting immune cells to prevent inflammatory response is the new direction of treatment for atopic dermatitis. Studies show that

Table 6. Costs of Protopic®

Strength	Amount	Cost
0.03% ointment	30 g	$ 69.64
0.03% ointment	60 g	$ 134.78
0.1% ointment	30 g	$ 72.74
0.1% ointment	60 g	$ 140.95

topical tacrolimus is not only effective in treating this disease, but also lacks the unpleasant adverse effects commonly seen with topical steroid therapy. While this may be a costly alternative to other available medications, overall topical tacrolimus seems to be an important clinical breakthrough for the treatment of atopic dermatitis.

References

1. American Academy of Dermatology. Patient Information: Eczema/Atopic Dermatitis. www.aad.org/pamphlets/eczema.html, 1999.
2. Clinical Pharmacology 2000. Tacrolimus/ Protopic Monograph.
3. Fugisawa Healthcare, Inc. Full Prescribing Information for Protopic. Dec 2000.
4. Fugisawa Healthcare, Inc. Professional Resources: Prograf Product Monograph. www.prograf.com/prof/dosageadm.asp#blood
5. Hanifin J, et al. Tacrolimus Ointment for the Treatment of Atopic Dermatitis in Adult Patients: Part I, Efficacy. *J Am Acad Dermatol* 2001;44(Suppl):S28-38.
6. Paller A, et al. A 12-Week Study of Tacrolimus Ointment for the Treatment of Atopic Dermatitis in Pediatric Patients. *J Am Acad Dermatol* 2001;44(Suppl):S47-57.
7. Kawakami T, et al. Safe and Effective Treatment of Refractory Facial Lesions in Atopic Dermatitis Using Topical Tacrolimus following Corticosteroid Discontinuation. *Dermatology* 2001;203:32-37.
8. Soter N, et al. Tacrolimus Ointment for the Treatment of Atopic Dermatitis in Adult Patients: Part II, Safety. *J Am Acad Dermatol* 2001;44(Suppl):S39-46.
9. Kang S, et al. Long-Term Safety and Efficacy of Tacrolimus Ointment for the Treatment of Atopic Dermatitis in Children. *J Am Acad Dermatol*;44(Suppl):S58-64

Treating Community-Acquired Pneumonia In the Drug Resistant Era

QueTran Hoang, Pharm. D. Candidate

Introduction

Antimicrobial resistance leads to increased mortality, morbidity, and health care costs. The emergence of drug-resistant pneumococcal strains has complicated the management of infections such as community-acquired pneumonia (CAP). Pneumonia currently constitutes the sixth cause of death and the first cause of infectious death in the United States.[1] *Streptococcus pneumoniae* is the most commonly identified cause of CAP, accounting for 9% to 55% of cases of community-acquired pneumonia among patients requiring hospitalization.[2] In the past, several agents have been used as first line treatment options for this organism in CAP. However, with extensive usage, in-vitro antimicrobial resistance has developed.[2,3] According to the National Committee for Clinical Laboratory Standards (NCCLS), in cases of pneumonia, *S. pneumoniae* should be considered as penicillin susceptible if the MIC is 0.06 g/mL, as intermediate susceptible if the MIC is 0.1 to 1.0 g/mL, and resistant if the MIC is 2.0 g/mL.[10] Unfortunately, resistance extends beyond the ß-lactam antibiotics. Resistance has been documented to other classes of antibiotic including the macrolides and the fluoroquinolones.[3,8,16] This article will review the role of ß-lactam antibiotics, macrolides, and the fluoroquinolones in the treatment of pneumococcal CAP.

Mechanism of Resistance

Bacteria possess a significant number of genetic mechanisms for resistance to antimicrobials. Three of the proposed mechanisms for resistance development that are influenced by antimicrobial usage include acquisition of resistance, emergence of dormant resistance and selection of resistant subpopulations. Resistance to penicillin is acquired through the production of ß-lactamase, altered penicillin-binding proteins (PBPs), and the reduction of permeability. Penicillin resistance in *S. pneumoniae* is intrinsic and appears to be caused by altered PBPs. Although the majority of strains with re-

duced susceptibility to penicillin are susceptible to certain third-generation cephalosporins, such as cefotaxime or ceftriaxone, intermediate resistance and resistant strains are increasing. Bacterial resistance to cephalosporins may be natural or acquired and may result from one or a combination of factors. A major mechanism of bacterial resistance to cephalosporins is the production of ß-lactamase which inactivates the drugs by hydrolyzing the ß-lactam ring. Nevertheless, absence or presence of a ß-lactamase does not entirely dictate susceptibility or resistance to a cephalosporin. Bacterial resistance usually results from both ß-lactamase production and presence of permeability barriers.[4,9,11,12]

Resistance to erythromycin from *S. pneumoniae* develops stepwise and is due to two main mechanisms: one involves the target site modification by an enzyme that methylates 23S rRNA, the erythromycin resistance methylase, and the second is the presence of a macrolide efflux pump. Efflux mutants, encoded by *mefE*, account for approximately 60-75% of macrolide-resistant strains of *S. pneumoniae* in North America.[8] This mechanism of resistance can be overcome with higher serum erythromycin concentrations. Cross-resistance does occur among the macrolides, including azithromycin, clarithromycin, dirithromycin, and erythromycin. Resistance by the mechanism of ribosomal methylase encoded by *ermAM*, which occurs mostly in Europe, results in a high grade of resistance that cannot be overcome. Erythromycin, specifically, exhibits a dissociated type of resistance, in which the presence of erythromycin can influence in vitro susceptibility testing. For example, strains of organisms that are resistant to erythromycin but susceptible to other macrolides may show resistance to these drugs if erythromycin was also present. Clindamycin's MIC is used to determine which macrolide resistance is present. *S. pneumoniae* resistance arising from ribosomal methylation is erythromycin resistant and clindamycin resistant, however, macrolide resistance from the efflux mechanism can be erythromycin resistant and clindamycin susceptible. *S. pneumoniae* strains, with *mefE* phenotype and MIC of erythromycin between 1 and 16 g/mL, are resistant to macrolides but susceptible to clindamycin. [3,4,8,11]

Fluoroquinolones (FQs) remain a popular choice of antibiotic for many inpatient and outpatient infections. Some fluoroquinolones possess excellent antipneumococcal activity. Unfortunately, with widespread use, resistance to this class of antibiotic has also emerged, therefore the Center of Disease Control (CDC) currently recommends fluoroquinolones as a second line treatment for CAP. The organisms become resistant to FQs through two mechanisms: chromosomal mutations or alterations in their ability to permeate the bacterial cell wall. Single or multiple mutations in the genes encoding the bacterial DNA gyrase or topoisomerase IV are the specific sites of mutation. *S. pneumoniae* shows resistant to FQs through the efflux pump mechanism, which limits intracellular accumulation of antimicrobials. This is independent of the FQs resistance caused by the other two mechanisms and is an energy dependent process. Cross-resistance among the FQs does exist, therefore empiric therapy with FQs should be used with caution.[4,6,10,11,13,16]

Pharmacokinetics

Amoxicillin has extended antibacterial activity to the gram-negative organisms and closely related to ampicillin. It has a more complete absorption than ampicillin, 74-92% absorption from a single dose, which results in higher serum concentrations. With a more complete absorption, less drug remains in the intestinal tract, and the frequency of diarrhea is decreased. Peak serum concentrations of amoxicillin are generally reached 1-2 hours after oral administration.[6, 11, 12]

Several cephalosporins such as cefuroxime, cefotaxime, cefepime, or ceftriaxone are also recommended for the treatment of CAP.[6,7] These agents have better coverage against *S. pneumoniae* compared to other cephalosporins. The bioavailability of cefuroxime is increased when taken with food. The variable absorption rate of this drug accounts for the high incidence of gastrointestinal side effects. Cefotaxime is unique among the cephalosporins since it is metabolized through deacetylation by the liver to a biologically active metabolite, desacetylcefotaxime. Desacetylcefotaxime in combination with cefotaxime can have synergistic or addictive effects. Ceftriaxone has the longest half-life of the ß-lactams. It is unique among the cephalosporins in that it is one of two cephalosporins that has a dual hepatic and renal ex-

Table 1. Overview of Pharmacokinetic Properties

Drugs	Dose	F (%)	$t_{1/2}$ (hours)	C_{max} (mg/L)	Excretion	Protein binding
Cephalosporins						
Cefuroxime	750 mg	50	1.3	4.1	Urinary	35%
Ceftriaxone	1 gm	----	8.5	132	Dual	83-96%
Cefepime	1 gm	----	2.0	29.6	Urinary	20%
Cefotaxime	1 gm	----	1.2	37.9	Urinary	35%
Macrolides						
Erythromycin	500 mg	15-45	2	3.0	Biliary	80%
Clarithromycin	500 mg	50	3-5	2.4-3.5	Biliary	42-50%
Azithromycin	500 mg	34	10-40	0.336	Biliary	52%
Fluoroquinolone						
Ciprofloxacin	500 mg	85	3-7	2.0	Urinary	35%
Levofloxacin	500 mg	99	7.4	5.2	Urinary	24-38%
Moxifloxacin	400 mg	90	12		Urinary	50%
Gatifloxacin	400 mg	98	8.4	3.4	Urinary	20%
Penicillin						
Amoxicillin	500 mg	74-92	0.7-1.4		Urinary	17-20%

F = bioavailability, C_{max} = maximal concentration, $t_{1/2}$ = half-life, < 95% protein binding considered insignificant, dual = biliary + urinary

cretion.[3, 6, 11]

Macrolide agents have some activity for organisms with penicillin MIC values of 2.0 mg/L, this may be due to the high degree of macrolide penetration into respiratory secretions. Most macrolide resistance in North America is due to an efflux mechanism. The efflux mechanism is associated with substantially lower MIC values than the ribosomal mechanism.[6] Clarithromycin and azithromycin have a broader coverage and are better tolerated compared to erythromycin. Erythromycin is well absorbed from the gastrointestinal tract (GIT). Erythromycin is excreted primarily in the bile. The normal serum half-life is 1.4 hours and serums levels are maintained for 6 hours. Clarithromycin is also well absorbed from the GIT with a bioavailability of 50% with steady state usually reached after five doses. Clarithromycin tissue-serum ratio is greater than erythromycin but less than azithromycin. It is extensively metabolized in the liver and excreted renally. Azithromycin is more stable than erythromycin at gastric pH. It has an extensive uptake from the circulation into intracellular compartments, followed by a slow release. Azithromycin is eliminated unchanged in the feces with no metabolite. It has a mean tissue half-life of 2-4 days, which allows a 5-day regimen for CAP.[3, 8, 12]

Antipneumococcal fluoroquinolones (FQs) such as moxifloxacin, levofloxacin, or gatifloxacin penetrate well into the lung, often achieving levels higher than serum levels at sites such as the epithelial lining fluid and alveolar macrophages. FQs have longer serum half-lives, which allows for once daily dosing and higher peak levels. FQs are bactericidal antibiotics and display a concentration-dependent killing effect. They also exhibit a post-antibiotic effect.[12] Table 1 reviews the pharmacokinetics properties of the FQs and other agents recommended for the treatment of CAP.

Clinical Studies

A prospective, open-labeled, multicenter, randomized, and actively controlled study enrolled 590 patients to compare the safety and efficacy of 7 to 14 days of levofloxacin treatment versus ceftriaxone and/or cefuroxime axetil for the treatment of CAP in adults. *S. pneumoniae* was the most common pathogen and was isolated from 63 sputum specimens (15% of patients that were clinically evaluated). After 5-7 days of therapy, levofloxacin had a higher success rate of 96% compared to the

ceftriaxone and/ or cefuroxime axetil success rate of 90%. Levofloxacin eradicated 100 % of *S. pneumoniae* while ceftriaxone and/or cefuroxime axetil eradicated 85% of the pathogen. Tolerability was similar in both groups with mild gastrointestinal symptoms being the most common. Even though levofloxacin shows an eradication rate of 100% for *S. pneumoniae* in this study, in areas with high rates of pneumococcal resistance, local sensitivity patterns need to be seriously considered. More recently, reserved use status of levofloxacin is recommended based on levofloxacin-resistant *S. pneumoniae* that was cross-resistant to newer fluoroquinolones.[18]

An international multicenter, randomized, prospective, double blind study compared the efficacy and safety of two oral moxifloxacin regimens and oral clarithromycin in the treatment of community-acquired pneumonia. *S. pneumoniae* was 42% of the isolated pathogens. A total of 678 patients were randomized to receive either moxifloxacin 200 mg qd, 400 mg qd, or clarithromycin 500 mg bid for ten days. Patients were evaluated for clinical and bacteriological response. Clinical success rate after 3-5 days post-therapy was 93.9% for patients treated with moxifloxacin 200 mg, 94.4% with 400 mg moxifloxacin, and 94.3% with clarithromycin. After 21-28 days of study treatment, clinical success rate of 200 mg moxifloxacin was 90.7%, 92.8% with 400 mg moxifloxacin, and 92.2% with clarithromycin. The bacteriological success rate for *S. pneumoniae* was 95% (200 mg moxifloxacin), 90.5% (400 mg moxifloxacin), and 91.7% (clarithromycin). Adverse events from this study are similar among the treatment groups. This study indicates that moxifloxacin is as effective and well-tolerated as clarithromycin. Bacteriological success rate is slightly higher in the moxifloxacin-treated patients than the clarithromycin-treated patients. Data from this study and other in vitro data have demonstrated moxifloxacin has a spontaneous mutation frequency in *S. pneumoniae* of 1 x 10^{-9}, two orders lower than other quinolones.

An open-labeled, randomized study evaluated the efficacy of azithromycin as monotherapy for the treatment of CAP in adults.[14] Azithromycin was administered to 414 patients: 202 comparative trial and 212 non-comparative trial. The azithromycin in each group was administered as 500 mg IV for 2-5 days, then followed with 500 mg PO for 7-10 days. The comparative trial was a multicenter, parallel group, randomized, open-labeled study with 202 patients received azithromycin compared to 201 patients treated with cefuroxime at 750 mg IV every 8 h for 2-7 days, followed by cefuroxime axetil at 500 mg PO every 12 h for a total of 7-10 days of therapy. In the non-comparative trial, patients were given the same dosing regimen as the comparative trial. Eighty-nine isolates of *S. pneumoniae* were detected, in which 15% had reduced susceptibility to penicillin and 5% had reduced susceptibility to azithromycin. Six patients with the reduced susceptibility *S. pneumoniae* were treated with azithromycin. Eradication rate for azithromycin in both trials combined was 64 of 67 (96%). The study demonstrated that initial azithromycin therapy had fewer side effects and comparable if not superior efficacy as cefuroxime therapy. Evidence from this study indicated that cephalosporins and macrolides still have a role in the treatment of CAP in the pneumococcal resistance era.

In a prospective, multinational, multicenter, double-blind, comparative study, 411 patients with suspected pneumococcal CAP were randomized 1:1 to receive either moxifloxacin 400 mg/d or amoxicillin 1000 mg tid for 10 days.[15] Ninety-eight of 362 patients that were able to be evaluated were positive for pneumococcal pneumonia. The clinical success rate at end of therapy (EOT) was 91.5% for moxifloxacin and 89.7% for amoxicillin; at follow up, 89.4% for moxifloxacin and 89.3% for amoxicillin. In both groups, five patients with pneumococcal pneumonia in each group had a bacteriologic response failure. Both of these drugs are well tolerated with similar number of adverse events. This study demonstrated that moxifloxacin 400 mg once daily for 10 days is as effective and well tolerated as high dose amoxicillin, 1000 mg tid for ten days, for the treatment of pneumococcal pneumonia. Table 2 summarizes the above studies.

Recommendations

According to the CDC guidelines for the treatment of out-patient CAP in the pneumococcal era, patients with mild to moderate CAP should be treated empirically with a macrolide (azithromycin, erythromycin, or clarithromycin), or an oral antipneumococcal ß-lactam such as cefuroxime axetil

Table 2. Summary of Clinical Trials of the Recommended Agents for the Treatment of CAP

Reference	Study design	N	Study Regimen	Duration (days)	Clinical Success (%)
File et al.[13]	MC, PR, R, OL	590	1. LEVO 500 mg IV or PO QD 2. CEFX (parenterally) 1 or 2 gm QD or BID and or cefuroxime axetil (orally) 500 mg BID	7-14	5-7 days post therapy success: LEVO: 96% CEFX: 90% Bacteriologic eradication: LEVO: 98% CEFX: 85%
Hoeffken et al.[17]	MN,MC, R, PR, DB	678	1. MOXI 200 mg QD 2. MOXI 400 mg QD 3. CLAR 500 mg BID	10	3-5 days post therapy: MOXI200mg: 93.9% MOXI400mg: 94.4% CLAR: 94.3%
Plouffe et al.[14]	OL, R,C	414	1. AZI 500 mg IV daily x 2-5 days, followed by 500 mg PO QD 2. CEFU 750 mg q8h for 2-7 days, followed by cefuroxime axetil 500 mg PO Q 12h	7-10	10-14 days post therapy: AZI: 77% cured rate CEFU: 74% cure rate
Petitpretz et al.[15]	MN, MC, DB, R	411	1. MOXI 400 mg PO QD 2. AMOX 1,000 mg PO TID	10	MOXI: 91.5 AMOX: 89.7

LEVO = levofloxacin, CEFX = ceftriaxone, AZI = azithromycin, CEFU = cefuroxime, MOXI = moxifloxacin, CLAR: clarithromycin, AMOX= amoxicillin, MC= multicenter, PR= prospective, R= randomized, OL= open-labeled, C= controlled, MN= multinational, DB= double blinded.

(500 mg BID) or a high dose amoxicillin (500 mg TID).[6] Due to an increasing rate of resistance to the fluoroquinolones and its broad spectrum of coverage, the guidelines recommend to reserve the antipneumoccocal FQs as an alternative for those who are allergic to other agents, or who have failed other regimens, or those with highly drug resistant pneumococci (penicillin MIC>4). Because of the toxicities observed in juvenile animals, the FQs are not approved for children. For children younger than 5 years old, a ß-lactam is the best choice. For intermediate susceptible strains of pneumococcus (MIC< 1 g/mL), ß-lactam antibiotics are still effective. In the absence of immediate hypersensitivity reactions, penicillin can be safely administered in high doses to overcome the intermediate susceptible pathogen.[4,6,9]

Erythromycin has a limited antimicrobial spectrum of activity and poorly tolerated due to gastrointestinal side effects. Azithromycin and clarithromycin have a better profile but are more expensive. About 5% of penicillin-resistant *S.*

Table 3. Adverse Drug Reactions

Drugs	Diarrhea	Nausea	Hypersensitivity	Headache	Phototoxicity	Hepatic Effects
Cefuroxime	4-10.6%	2-7%	5%	rarely	-----	1%
Ceftriaxone	2-4%	<1%	<1%	<1%	-----	3%
Cefepime	2%	2%	4%	1%	-----	-----
Cefotaxime	1%	1%	2%	<1%	-----	<1%
Erythromycin	7-15%	4-7%	1%	<1%	-----	4.7%
Azithromycin	5-7%	4.3%	1.9%	<1%	-----	1-2%
Clarithromycin	2%	3%	1%	2%	-----	<1%
Ciprofloxacin	2-10%	2-10%	1-4%	1-2%	<1%	2%
Levofloxacin	2-4%	2-4%	2%	1%	<1%	2%
Gatifloxacin	3%	2%	1-4%	1%	1%	2.5%
Moxifloxacin	1-2%	1-2%	.05-1%	<1%	<1%	2%
Amoxicillin	9-17%	8%	1.4-10%	rarely	-----	rarely

Table 4. Drug interactions with the FQs[12]

	Gatifloxacin	Moxifloxacin	Levofloxacin	Ciprofloxacin
Antacids	Yes	Yes	Yes	Yes
Vitamins/minerals	Yes	Yes	Yes	Yes
Theophylline	No	No	No	Yes
NSAIDs	No	No	Yes	Yes?
Warfarin	No	No	No	Yes
Digoxin	No	No	No	No
Drugs with prolong QT interval	Yes	Yes	Yes	N/A

pneumoniae are resistant to macrolides in vitro. When choosing an agent for the treatment of pneumococcal pneumonia, one not only need to consider the coverage spectrum, but also the cost of therapy and the tolerability profile.

Finally, all clinicians are advised of recently adopted supplemental MIC breakpoints for non-meningeal sources of *S. pneumoniae* to both cefotaxime and ceftriaxone. Resistant isolates are now defined as MIC's = 4 mcg/cc. All labs should implement this change immediately. Based on the new MIC's, ceftriaxone is expected to be 96-97% effective against all strains of *S. pneumoniae*.

Adverse Reactions

The side effects of the antimicrobial agents are summarized in Table 3. Gastrointestinal disturbance is common among the antibiotics. Phototoxicity is common in the fluoroquinolones family.[12]

Drug Interactions

The absorption of all FQs can be interfered by the co-administration of divalent or trivalent cation-containing agents such as aluminum, magnesium, iron, calcium, and zinc containing products. A summary of relevant drug interactions is provided on Table 4. Drugs that are metabolized by the cytochrome P450 isoenzyme family can be altered as some of the macrolides are inhibitors of this system. Concomitant administration of clarithromycin and carbamazepine can cause an elevation of carbamazepine levels. Other potential interactions include theophylline, caffeine, digoxin, triazolam, ergotamine, cyclosporine, warfarin, valproate, midazolam, and terfenadine. With the ß-lactam antibiotics, caution should be noted with drugs that have potential for nephrotoxicity such as chloramphenicol, aminoglycosides, or cyclosporine, etc…

Cost

A summary of the average cost of the above antimicrobial agents for outpatient treatment of CAP is provided in Table 5.

Summary

S. pneumoniae is the most common cause of CAP worldwide. Drug therapy for the treatment of CAP in the era of pneumococcal resistance was reviewed including its mechanisms of resistance to the most commonly used antibiotics. For the treatment of penicillin susceptible and intermediate resistant (MIC<1) pneumococcus, amoxicillin and cephalosporins are an appropriate choice. Macrolides are a reasonable alternative, however, resistance has also increased rapidly in this class within the last decade but can be overcome with higher dosing. For highly resistant strains (MIC>2), a fluoroquinolone should be used, although cost of therapy and risk of increasing resistance should seriously be taken into consideration. As drug resistance rapidly rising, more studies are recommended for evaluation of the most appropriate regimen in the era of pneumococcal resistance.

Table 5. Cost Comparison for 10 days Treatment

Agents	Dose	Cost
Erythromycin	250 mg QID	$11.95
Clarithromycin (Biaxin)	500 mg BID	$95.12
Azithromycin (Zithromax)	500 mg QD	$115.84
Levofloxacin (Levaquin)	500 mg QD	$95.08
Ciprofloxacin (Cipro)	500 mg BID	$118.77
Moxifloxacin (Avelox)	400 mg QD	$101.85
Gatifloxacin (Tequin)	400 mg QD	$92.45
Amoxicillin	1 gm TID	$28.70
Cefuroxime axetil (Ceftin)	500 mg BID	$169.95

References

1. Barlett JG, Mundy LM. Community acquired

Pneumonia. *N Engl J Med* 333: 1618-24, 1995.
2. Bochud, PY et al. "Community- acquired Pneumonia: A Prospective Study." *Medicine* March 2001; 80(2).
3. Amsden, GW. "Pneumococcal Macrolide Resistance- Myth or Reality." *Journal of Antimicrobial Chemotherapy* 1999; 44:1-6.
4. Heffelfinger, JD et al. "Management of Community-Acquired Pneumonia in the Era of Pneumococcal Resistance" A report from the Drug-Resistant Streptococcus Pneumoniae Therapeutic Work Group. *Archives of Internal Medicine* May 22,2000; 160: 1399-1408.
5. Marie TJ. Community-Acquired Pneumonia: Epidemiology, Etiology, Treatment. *Infect Dis Clin North Am*. 1998; 12:723-740.
6. Barlett, JG et al. "Practice Guidelines for the Management of Community-Acquired Pneumonia in Adults." Guidelines from the Infectious Disease Society of America. *Clin Inf Dis* 2000;31:347-82.
7. Kaplan SL, et al. Management of Infections due to Antibiotic-Resistant Strep. Pneumoniae. *Clin Microbiol Rev* 1998;11: 628.
8. J Garau. "The Clinical Impact of Macrolide Resistance in Pneumococcal Respiratory Infections. *International Journal of Antimicrobial Agents* September 2001; 18(1): 33-38.
9. Shales, DM et al. " Society for Healthcare Epidemiology of America and Infectious Disease Society of America Joint Committee on the Prevention of Antimicrobial Resistance in Hospitals." *Clin Inf Dis* 1997;25:584-99.
10. Guidelines for the Management of Adults with Community Acquired Pneumonia by the American Thoracic Society. *Am J Respir Crit Care Med* 2001; 163:1730-1754.
11. Harwell, JI. "The Drug-Resistant Pneumococcus: Clinical Relevance, Therapy, and Prevention." *Chest* February 2000; 117(2): 530-541.
12. Mandell, LA. "Antibiotic Therapy for Community-Acquired Pneumonia" *Clinics in Chest Medicine* September 1999;20(3): 589-98.
13. File et al. "A Multicenter, Randomized Study Comparing the Efficacy and Safety of Intravenous and/or Oral Levofloxacin versus Ceftriaxone and/or Cefuroxime Axetil in Treatment of Adults with Community Acquired Pneumonia." *Antimicrobial Agents and Chemotherapy* September 1997; 41(9): 1965-1972.
14. Plouffe J. et al. "Clinical Efficacy of Intravenous Followed by Oral Azithromycin Monotherapy in Hospitalized Patients with Community Acquired Pneumonia." *Antimicrobial Agents and Chemotherapy* July 2000; 44(7): 1796-1802.
15. Petitpretz, P et al. "Oral Moxifloxacin vs. High Dosage Amoxicillin in the Treatment of Mild-to-Moderate, Community-Acquired, Suspected Pneumococcal Pneumonia in Adults." *Chest* January 2001; 119: 185-195.
16. Chen, DK et al. "Decreased Susceptibility of S. pneumoniae to Fluoroquinolones in Canada". *N Eng J Med* July 1999;341(4):233-239.
17. Hoeffken G et al. "The Efficacy and Safety of Two Oral Moxifloxacin Regimens Compared to Oral Clarithromycin in the Treatment of Community-Acquired Pneumonia." *Respiratory Medicine* 2001 95; 553-564.
18. Davidson R et al. "Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. *N Engl J Med* 2002 7;346(10):747-50.

The PharmaNote is Published by:
The Department of Pharmacy Services, UF Family Practice Medical Group, Departments of Community Health and Family Medicine and Pharmacy Practice University of Florida