Published in final edited form as:

Expert Opin Pharmacother. 2017 August ; 18(11): 1039–1048. doi:10.1080/14656566.2017.1340937.

MANAGING COMMUNITY ACQUIRED PNEUMONIA IN THE ELDERLY – THE NEXT GENERATION OF PHARMACOTHERAPY ON THE HORIZON

B Amalakuhan, KL Echevarria, and MI Restrepo*

University of Texas Health Science Center San Antonio (San Antonio, TX, USA) South Texas Veterans Health Care System (San Antonio, TX, USA)

Abstract

INTRODUCTION—Community acquired pneumonia (CAP) is associated with high rates of morbidity and mortality, especially among the elderly. Antibiotic treatment for CAP in the elderly is particularly challenging for many reasons, including compliance issues, immunosuppression, polypharmacy and antimicrobial resistance. There are few available antibiotics that are able to address these concerns.

AREAS COVERED—After a systematic review of the current literature, we describe seven novel antibiotics that are currently in advanced stages of development (phase 3 and beyond) and show promise for the treatment of CAP in those over the age of 65. These antibiotics are: Solithromycin, Pristinamycin, Nemonaxacin, Lefamulin, Omadacycline, Ceftobiprole and Delafloxacin. Using a novel conceptual framework designed by the present authors, known as the ‘San Antonio NIPS model’, we evaluate their strengths and weaknesses based on their ability to address the unique challenges that face the elderly.

EXPERT OPINION—All seven antibiotics have potential value for effective utilization in the elderly, but to varying degrees based on their NIPS model score. The goal of this model is to reorganize a clinician’s focus on antibiotic choices in the elderly and bring attention to a seldom discussed topic that may potentially become a health-care crisis in the next decade.

Keywords

CAP; Ceftobiprole; community-acquired pneumonia; Lefamulin; Nemonaxacin; Omadacycline; pharmacotherapy; Pristinamycin; San Antonio NIPS Model; Solithromycin

* **Corresponding Author:** Marcos I. Restrepo, MD, MSc; South Texas Veterans Health Care System ALMD - 7400 Merton Minter Boulevard - San Antonio Texas, 78229; Phone: (210)-617-5300 ext. 15413 - Fax: (210) 567-4423; restrepom@uthscsa.edu.

Secondary Author Contact: Bravein Amalakuhan, MD; University of Texas Health Science Center at San Antonio; 7703 Floyd Curl Drive - San Antonio, Texas, 78229; Phone: (210)-567-4928, Fax: (210) 567-1976; Amalakuhan@uthscsa.edu.

Author Contributions: All authors contributed to the conception and design of this review paper, as well as revising it critically for its intellectual content. All authors provided approval of this manuscript for final publication.

Declaration of Interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed

[1] INTRODUCTION

Community acquired pneumonia (CAP) is associated with a high rate of morbidity and mortality, inflicting more than 5 million patients each year, and costing the US health-care system 12-billion dollars annually.¹⁻³ These rates are even higher among the elderly, with CAP being the sixth leading cause of death among those over the age of 65.^{2, 3} More than 20% of the U.S. population is currently over the age of 65, and this is expected to increase over the next decade as the baby-boomer generation ages.⁴ As a consequence, there will be an even further rise in the incidence CAP world-wide, as well as health-care expenditure and mortality among this vulnerable population.² It is worth mentioning that CAP is not a required reportable disease, and thus these statistics are likely a gross underestimation of the health care burden that this disease actually poses. Considering these alarming numbers, further research is needed to study this population and their unique characteristics, to tailor specific treatments and improve outcomes.

One central aspect of treatment of CAP in any population, including the elderly is the use of antibiotics. There is a clear association established between early appropriate antibiotics and improved outcomes, especially among the elderly.¹ However, choice of antibiotics in this patient population is a complex topic that has not been well studied. Given limited data, the current CAP guidelines do not recommend different antibiotic regimens for the elderly.^{1, 5} Nonetheless, this population has a number of unique characteristics that make antibiotic choices challenging. First, they have higher rates of cognitive deficits making compliance a concern, especially when using antibiotics with more frequent dosing intervals. Second, advanced age has been shown to be associated with relative immunosuppression, including reduced production of B and T lymphocytes and diminished function of mature lymphocytes.^{6, 7, 8} As a result, the elderly have a decreased ability to fight off infections compared to their younger counterparts.⁷ Third, polypharmacy is frequent in the elderly population due to pre-existing medical conditions, which can result in medication side-effects and drug-drug interactions that impact tolerance and compliance.⁹ Finally, in 2011 the 'Centers for Disease Control and Prevention' (CDC) identified antimicrobial resistance as a serious global health concern. Those over the age of 65 have higher rates of multi-drug resistant (MDR) organisms due to their greater cumulative exposure to previous antibiotics and more frequent contact with the health care system.⁷ Consequently, this patient population is more difficult to treat because antibiotic choices are limited.⁹ There are currently few antibiotics available that are able to address all these unique challenges. As a result, the study of newer classes of antibiotics to address these concerns are key to improving outcomes.

Understandably, there is an immense need for the development of new antibiotics, especially in the context of the aging population and those over the age of 65. To address this growing necessity, a conceptual framework is required to help direct clinicians when determining the optimal antibiotic choice for this patient population and to guide future antibiotic research in the elderly. Ideally, the elderly population will require antibiotics with four key characteristics, which the present authors have organized into a novel and simplistic paradigm known as the 'San Antonio NIPS Model' (N for novelty of mechanism, I for avoidance of interactions and intolerance, P for favorable pharmacokinetic/pharmacodynamic profiles, and S for simplicity of dosing). First, newer antibiotics will need

to have a novel mechanism of action, allowing them to treat CAP cases due to bacteria that have developed resistance to other antibiotics. Furthermore, they will also need to be relatively immune to the development of resistance since elderly patients have more frequent exposure to antibiotics. Second, these antibiotics should have low rates of side effects and minimal drug-drug interactions. Third, they should have favorable pharmacokinetics and pharmacodynamics, allowing for more effective bacterial eradication in this vulnerable population. Fourth, since impaired cognition is common in the elderly, these antibiotics should ideally have longer half-lives with less frequent dosing intervals, ensuring simple dosing regimens that may improve adherence. Table 1 describes this scoring system in more detail.

There are a number of new antibiotics that exhibit many of the four key characteristics described above. Some have been recently approved for CAP while others are in late-stage development (phase 3 and higher). The antibiotics discussed below were selected after extensive review of the literature, and after screening for their applicability to the elderly and their relative strengths based on the NIPS Model described above. Seven new antibiotics are presented, including their mechanism of action, spectrum of activity, pharmacokinetic / pharmacodynamics (PK/PD) profiles, stage of clinical development and their relative value to the elderly population based on the NIPS Model.

[2] THE NEXT GENERATION OF NEW ANTIBIOTICS

[2.1] SOLITHROMYCIN:

[2.1.1] Pharmacology: Solithromycin is a novel fourth generation macrolide, and the first fluoroketolide in development.¹⁰ Macrolides exert their activity by binding to the 23S ribosomal RNA (rRNA), inhibiting protein synthesis. Its spectrum of coverage includes many organisms commonly associated with CAP, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Legionella pneumophila*, *Mycoplasma pneumoniae* and MSSA. Solithromycin's ability to bind to an additional site on rRNA differentiates it from other macrolides, resulting in activity against many macrolide-resistant *S. pneumoniae*.¹⁰ Of note, it is also active in-vitro against MRSA, giving it broader activity compared to the previous generations of macrolides.^{10, 11} From a PK perspective, it is available in both oral and intravenous formulations.¹⁰ Its bioavailability is 67% when given orally and not influenced by concomitant food intake.¹⁰ Its serum protein-binding is 81%, and with a biologic half-life of 8.5-hours it can be dosed once daily.¹⁰ There is approximately 20% first-pass metabolism in the liver and GI tract, but is mainly metabolized by the CYP3A4 pathway.¹⁰ Its metabolites are excreted predominantly in bile and the GI tract, with a minor amount excreted via the renal route (14%).¹⁰ Pharmacodynamically, solithromycin is 16-times more potent than azithromycin, clarithromycin and telithromycin against gram-positive aerobes, as well as atypical and gram negative CAP pathogens.¹⁰

[2.1.2] Clinical Background: Solithromycin recently completed phase 3 trials for the treatment of patients with mild and moderately severe CAP (Port Scores II-IV).^{11, 12} In two separate multicenter, global, double-blind, randomized controlled, non-inferiority trials, researchers compared oral solithromycin to oral moxifloxacin in patients with CAP, with the

primary end-point being early clinical response.^{11, 12} Exclusion criteria included mainly previous antibiotic use and patients who were currently immunosuppressed. Solithromycin was found to be non-inferior to moxifloxacin for the primary end points with 860 patients to the two groups in each of the two trials.^{11, 12} Regarding efficacy in elderly patient, 35% of patients enrolled were over the age of 65, with 15% over the age of 75.^{11, 12} In those over the age of 75, use of solithromycin was associated with numerically greater success rate and earlier clinical response compared to controls, although this difference did not reach statistical significance.^{11, 12} Side effects are mild and relatively low in frequency, consisting mainly of diarrhea (4%), nausea (4%) and headaches (4%).¹³ Of important note, it is the only macrolide that has been shown not to significantly prolong QT intervals.¹³ Hepatic safety however remains a concern. 5–10% of patients experience mild transaminase elevations and considering the relatively small sample sizes on which solithromycin was studied, the U.S. FDA believes this may be a potential underestimation of the safety risk. For this reason, on December 29th 2016, the U.S. FDA declined to approve its use for patients with CAP, mainly out of prior experience with another macrolide in its class (telithromycin) whereby severe hepatotoxicity was only observed after market approval with more widespread clinical use. This adverse event led to the withdrawal of telithromycin from the market in 2007. Although there were no cases of acute severe liver injury and only transient elevations in liver enzymes reported in the above studies with solithromycin, the FDA recommended further studies to evaluate the risk of hepatic toxicity before formal approval. Specifically, U.S. FDA is requesting that its pharmaceutical company, Cemptra conduct a further study with 9000 patients to evaluate the potential for severe hepatic toxicity. Although Cemptra is appealing this requirement, if it fails to succeed, patients are unlikely to have solithromycin as a potential therapeutic option for the treatment of CAP in the near and foreseeable future Furthermore, they also requested that manufacturing related deficiencies at its participating sites be resolved, although details of these specific deficiencies are unknown. Solithromycin has already applied for approval with the EMA, but formal approval status in the European Union is still pending.

[2.1.3] The NIPS Model: Value to the Elderly: Solithromycin has many strengths to offer the elderly population based on the NIPS model, however important concerns exist. Its additional ribosomal binding sites give it a unique mechanism of action, providing it with activity against resistant organisms such as macrolideresistant *S.pneumoniae* and MRSA. The potential for emergence of resistance appears to be low due to low rates of spontaneous mutations in various bacterial organisms in-vitro, although further clinical studies are required to confirm this.¹³ Due to its inhibition of the CYP3A isoenzyme pathway it has frequent drug-drug interactions like other macrolides such as erythromycin and clarithromycin. Side effects are mild and relatively low in frequency, however there are concerns of severe hepatic toxicity that require further evaluation.¹³ In terms of renal impairment, dose adjustments are only needed for severe renal impairment providing it with more flexible dosing properties in various clinical settings.¹³ Third, it has a favorable PK profile, and from a PD perspective, it is highly potent with effective bactericidal properties and eradication rates.¹³ Lastly, its dosing regimen is simplistic, requiring only once-per-day dosing, maximizing the opportunity for adherence. Overall, solithromycin has a moderate NIPS model score, with activity against MDR organisms, high potency and a relatively

simple dosing regimen of only once per day. However, concerns over potential hepatic toxicity have delayed its approval by the U.S.FDA and the EMA, and drug-drug interactions remain problematic.

[2.2] PRISTINAMYCIN:

[2.2.1] Pharmacology: Pristinamycin is part of the streptogramin group of antibiotics, and is a mixture of two components: 1)Pristinamycin IA, which is a macrolide with similar activity to erythromycin and 2)Pristinamycin IIA (streptogramin A), a depsipeptide. Each component is bacteriostatic when used alone, but together their synergism results in irreversible binding to its targets, resulting in bactericidal activity that can reach up to 100 times that of each individual component.¹⁴ Its spectrum of coverage is similar to other macrolides, but also includes activity against macrolide resistant staphylococcal and streptococcal species, including MRSA.¹⁴ Few published reports exist regarding pristinamycin's pharmacokinetic profile, with its bioavailability, extent of protein binding in the serum, drug-drug interactions and route of excretion being unknown.¹⁵ Due to its poor solubility in water, it is only available in the oral form.¹⁵ The literature that is available show that it has a relatively short half-life of 5–7 hours, requiring three-times-per dosing, that and it is metabolized by the CYP3A4 pathway.¹⁵ Pharmacodynamically, in-vitro it is 100 times more potent than previous generations of macrolides, providing it with more effective bacterial eradication rates. Furthermore, studies have shown it to have higher potency and cure rates compared to beta-lactam antibiotics for various common CAP pathogens.¹⁴

[2.2.2] Clinical Background: Despite little being known about its pharmacokinetics, it has been in use for more than 50 years in Europe for soft tissue and joint infections. But data is beginning to accumulate as to its clinical effectiveness in patients with pneumonia. A previous multinational, randomized, double blind, non-inferiority trial with 400 patients, 25% of which were over the age of 65, reported that pristinamycin was non-inferior to amoxicillin for the treatment of CAP with cure rates of 80% and 83% respectively.¹⁶ Both antibiotics also had minimal adverse effects, mainly consisting of mild GI symptoms such as nausea, vomiting and diarrhea.¹⁶ However, 85% of the patients in this study had only mild CAP (Port Scores II and III). Researchers are currently conducting a multi-center, randomized, double-blind, non-inferiority phase 4 trial comparing pristinamycin to amoxicillin in CAP patients with PORT risk scores of II-III ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02332577) identifier: NCT02332577).¹⁷ The most notable exclusion criteria that may limit its generalizability appears to be its exclusion of patients with moderate and severe forms of CAP (PORT risk scores of at least group IV). Considering its lack of intravenous formulation, its unlikely it will ever have a role in patients with severe CAP. It is currently not yet formally approved by the U.S. FDA or the EMA for use in patients with CAP

[2.2.3] The NIPS Model: Value to the Elderly: The assessment of pristinamycin via the NIPS model highlights many drawbacks for utilizing this antibiotic in the elderly population. One strength is that it has a novel mechanism of action, providing it with activity against various resistant organisms. Pristinamycin has also been shown to have low rates of resistance development despite being used in Europe for more than 50 years for soft-tissue and joint infections, which is promising for its application in elderly patients with CAP.¹⁸

Clinical studies found low rates of side effects, demonstrating a good safety profile.¹⁴ However, it inhibits the CYP3A isoenzyme pathway and has many common drug-drug interactions. From a PD perspective, although also has a high potency of activity compared to beta-lactams, little is known about its pharmacokinetics making it not an ideal choice in the setting of the complex milieu of the elderly population.¹⁴ Furthermore, it is only available in the oral route, and thus it may not be ideal in patients with moderate and severe CAP who require intravenous administration or in clinical scenarios that preclude oral administration. From a simplicity perspective, it has three-times-per-day dosing and thus its dosing regimen is not ideal for maximizing compliance. Overall, pristinamycin has a low NIPS model score for the above reasons. We believe, that although preliminary clinical data does show promise, further data is needed before it can find a niche in this specific patient population.

[2.3] NEMONAXACIN

[2.3.1] Pharmacology: Nemonaxacin is a novel non-fluorinated quinolone with a methoxy group replacing the fluorine residue at the C-8 position, allowing this drug to target both topoisomerase II and IV, giving it an improved spectrum of activity, more effective pharmacodynamics, reduced mutant selection and potentially less toxic side-effects.¹⁹ It has a broad spectrum of activity against grampositive bacteria, being 4-times more active than classical fluoroquinolones such as levofloxacin and ciprofloxacin, with activity against MRSA and quinolone-resistant *S.pneumoniae*.^{19, 20} It also appears to be equally active against gram-negative CAP organisms compared to other fluoroquinolones.^{19, 20} Regarding PK, nemonaxacin has nearly 100% bioavailability, and is available in both oral and intravenous forms.²⁰ It has low serum protein binding at 16%, and a biologic half-life of nearly 19 hours.²⁰ Nemonaxacin does not appear to be metabolized, and is excreted unchanged in the kidneys over 24–72 hours.²⁰

[2.3.2] Clinical Background: Clinically, nemonaxacin has been evaluated in phase 2 trials in patients for diabetic foot ulcers, however for this indication it is still early in the development phase.²¹ However, clinical data is more abundant for Nemonaxacin in CAP. In a recent phase 3 multicenter, randomized, double blind, non-inferiority trial completed in Taiwan, the efficacy and safety of nemonaxacin was compared to levofloxacin in adult patients with mild and moderately severe CAP (PORT scores II-IV).²² Of important note, the study included patients up to the age of 70, with exclusion criteria consisting mainly of those with prior antibiotic use and patients who were currently immunosuppressed.²² A total of 532 patients were included in the study, and nemonaxacin was found to be non-inferior to levofloxacin, with clinical cure rates of 94% in both groups. There were also few side-effects, of which most were mild and similar in both groups.²² These results were only published in abstract form, however based on these results nemonaxacin has been approved for use by regulatory agencies in China, Taiwan, the Russian Federation, Turkey and Latin America for adult patients with CAP. A second phase 3 multicenter, randomized, double blind, non-inferiority trial has completed enrollment with goals to publish the results in the near future ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02205112) identifier: NCT02205112).²³ Notable inclusion criteria include patients up to the age of 80, with similar exclusion criteria to the previous study. In terms of side-effects, reports show that it is well tolerated with low rates of mild-side effects,

mainly nausea (8%), diarrhea (5%), dizziness (6%), and headaches (5%).²⁴ No clinically significant change in QT-intervals were noted as well.^{20, 24} Nemonoxacin has not yet obtained formal approval by the U.S. FDA or the EMA, however the results of this second phase 3 trial may bring it closer to achieving this. It has already received priority review status by the U.S. FDA, and will undergo an expedited regulatory approval process in the US for this indication once further phase III studies are available documenting its safety and efficacy.

[2.3.3] The NIPS Model: Value to the Elderly: Based on the NIPS model, nemonoxacin has a favorable profile for utilization in the elderly population. First, it has a novel mechanism of action providing it with activity against resistant bacterial organisms. Furthermore, Nemonoxacin requires three separate gene mutations compared to only 2 mutations required to confer resistance to the classical fluoroquinolones.²⁵ Consequently, nemonoxacin has a far less propensity to select for resistant pathogens in-vitro, which is promising. Second, it does not interact with cytochrome P450 isoenzymes and has a low propensity for serum protein binding, thus it has minimal potential drug-drug interactions.¹⁹ For similar reasons, it is also tolerated well with low rates of mild side-effects.²⁴ Third, it also has favorable pharmacodynamics, having higher potency for classical CAP pathogens compared to other fluoroquinolones.^{19,20,25} Furthermore, it has favorable pharmacokinetics, including excellent oral bioavailability, providing it with advantages in the outpatient setting. Finally, it has a simplistic dosing regimen, requiring only once per day dosing. Overall, nemonoxacin has a high NIPS model score, and coupled with data showing its clinical efficacy in elderly patients with moderate-severe CAP, we believe this antibiotic has great potential and a potential niche for use in the elderly population.

[2.4] LEFAMULIN:

[2.4.1] Pharmacology: Lefamulin is a novel semi-synthetic drug which is part of the pleuromutilin class of antibiotics.²⁶ It was previously utilized in veterinary medicine, with its uniqueness stemming from its ability to selectively inhibit bacterial protein synthesis by binding to the peptidyl transferase component of the 50S subunit of ribosomes.²⁶ This binding site is unique to this specific class of antibiotics. Lefamulin has potent bactericidal activity against typical and atypical bacteria, including gram-positive and gram-negative pathogens commonly associated with CAP. Because of its novel mechanism of action, it has potent in-vitro activity against organisms resistant to macrolides, fluoroquinolones, tetracyclines, vancomycin and B-lactam antibiotics.²⁶ In terms of its route of administration, it is available in both oral and intravenous forms. There are few published reports regarding lefamulin's pharmacokinetic profile, with the exact oral bioavailability unknown, although it is quoted as being "high".²⁷ It is 80% protein bound in the serum, has a biologic half-life of 12-hours and is largely excreted via the GI tract (86%) in its unchanged form, with the remaining eliminated via the kidney (14%).²⁷ Pharmacodynamically, it has a 4-times lower MIC₉₀ than oxacillin, vancomycin, linezolid, and ceftaroline for staphylococcus aureus species (including MRSA), and many other common CAP pathogens, making it highly potent.²⁸

[2.4.2] Clinical Background: Lefamulin has successfully completed phase 2 clinical trials providing evidence as to its efficacy and tolerability in patients with soft tissue infections, however it has reached more advanced stages of development in adult patients with CAP.²⁹ It is currently undergoing two phase 3, multi-center, randomized, double-blind, non-inferiority controlled trials to compare its efficacy and safety with moxifloxacin for adult patients with mild and moderately severe CAP, associated with PORT scores of II-IV ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT02559310 & NCT02813694).^{30, 31} Of note, 50% of the patients in the above trials are expected to be over the age of 65.^{30, 31} The primary end-point in these trials is early clinical response, with exclusion criteria mainly consisting of previous antibiotic use and patients who are currently immunosuppressed.^{30, 31} In terms of reported side effects, studies show that they mainly consist of headaches (7%), nausea (7%) and diarrhea/vomiting (4%).^{32, 33} Lefamulin received fast track status by the FDA providing it with an expedited regulatory approval process in the US once the above phase 3 trials are completed. It is currently not yet formally approved by the U.S. FDA, EMA or other regulatory agencies for use in patients with CAP.

[2.4.3] The NIPS Model: Value to the Elderly: Based on the NIPS model, lefamulin has important strengths and weaknesses. Lefamulin has a novel mechanism of action and is the first in its class to be approved for systemic use in humans, with activity against many multi-drug resistant organisms. Furthermore, in-vitro studies show that it has low rates of resistance development due to very low spontaneous mutation frequencies at sub-MIC levels.²⁶ This is confirmed by the fact that despite this antibiotic being in use for more than 30 years in veterinary medicine, a very low resistance rate has been observed.³³ Second, in-vitro studies have shown that although it inhibits the CYP3A pathway, this inhibition was apparently weak and overall required no dose adjustments when given with other medications that use the same pathway such as azole antifungals and midazolam.^{32, 33} Coupled with its high protein binding capacity however, potential drug-drug interactions with other medications are still a concern. Studies show that it has a favorable safety and tolerance profile due to its unique nucleotide binding pocket conferring an ability to be highly selective for bacterial ribosomes over human ribosomes. Side effects as a result are mild and occur at low rates.^{32, 33} Third, it has a favorable PK profile, and a similar favorable pharmacodynamics profile with a high potency for common CAP pathogens and other drug-resistant organisms.^{28, 32, 33} Lastly, although IV dosing is required only once per day, the oral route requires twice per day dosing. Overall, lefamulin has a moderate NIPS model score, due in part to its high degree of serum protein binding and its interaction in the CYP system.

[2.5] OMADACYCLINE:

[2.5.1] Pharmacology: Omadacycline is an antibiotic that is part of a new class of compounds known as aminomethycyclines.³⁴ Although they are related to the tetracyclines which inhibit bacterial protein synthesis in the same regard, they have unique properties due to small changes in their chemical structure that allow them to overcome both the efflux and ribosomal protection mechanisms that confer tetracycline resistance to bacteria.³⁴ Omadacycline has a broad spectrum of activity against typical and atypical bacteria, including common gram-positive and gram-negative CAP pathogens, as well as aerobes and

anaerobes.³⁵ It also has in-vitro activity against many resistant organisms, including MRSA and other multi-drug resistant bacteria including those classically resistant to tetracyclines.³⁵ It is available in both oral and intravenous forms, but oral bioavailability is only 35%.³⁶ It is 20% protein bound in the serum, with a biologic half-life of 17 hours, and is excreted un-metabolized in its active form through the kidneys and the GI tract. Pharmacodynamically, it is highly potent, having a three to five times lower MIC₉₀ than vancomycin and linezolid for tetracycline sensitive staphylococcus species, and having a nine times lower MIC₉₀ for MRSA and other resistant strains.³⁷

[2.5.2] Clinical Background: From a clinical perspective omadacycline has received fast track status by the FDA, and has successfully completed a phase 3 trial providing evidence as to its efficacy and safety in patients with soft tissue infections when compared to linezolid.³⁸ Researchers are currently enrolling in omadacycline's first phase 3 clinical trial for patients with CAP. This study is a multicenter, randomized, double-blind, non-inferiority trial comparing PO/IV omadacycline to PO/IV moxifloxacin in adults with mild, moderate and severe CAP ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02531438) identifier: NCT02531438).³⁹ A significant proportion of the enrolled patients are expected to be over the age of 65, with exclusion criteria consisting mainly of previous antibiotic use and patients who are currently immunosuppressed. In terms of side-effects, reports include nausea (17%), headache (13%), constipation (6%), dizziness (6%), and vomiting (6%).³⁵ Omadacycline is currently not yet formally approved by the U.S. FDA or the EMA for use in patients with CAP.

[2.5.3] The NIPS Model: Value to the Elderly: Based on the NIPS model, omadacycline has a favorable profile when considering its use in the elderly, although concerns still exist. First, it has a novel mechanism of action, allowing it to overcome many MDR organisms.³⁷ Second, it does not interact with the cytochrome P450 isoenzymes and is minimally protein bound in the serum and thus has few medication interactions.³⁷ Although there are few reports of severe side-effects, overall minor side-effects are relatively common, with nausea and headache being the most common. Third, it does however have a strong PD profile, being highly potent especially against resistant CAP pathogens. Furthermore, higher dosing levels and the outcomes of upcoming phase 3 safety and efficacy trials may circumvent concerns over its relative low oral bioavailability.³⁷ Omadacycline also has a simple dosing regimen, with once-daily dosing for the treatment of CAP. Omadacycline has a moderate NIPS model score, with limitations due largely to its frequent side-effects.

[2.6] CEFTOBIPROLE:

[2.6.1] Pharmacology: Ceftobiprole is a beta-lactam and the first in a new generation of extended spectrum cephalosporins.⁴⁰ Like other beta-lactams it binds to penicillin-binding proteins (PBP's), inhibiting transpeptidation and formation of the bacterial cell wall, leading to cell lysis and death resulting in potent bactericidal activity.⁴⁰ Its novel property stems from its ability to bind to several different PBPs on a single bacterial organism, forming a unique inhibitory complex, providing it with activity against beta-lactam resistant organisms.⁴⁰ Ceftobiprole has activity against common gram positive and gram negative CAP pathogens, as well as clinically important organisms such as *Pseudomonas aeruginosa*, and resistant organisms such as MRSA.⁴⁰ Due to its limited and almost negligible oral

bioavailability, it is only available in the intravenous form.⁴¹ Pharmacokinetically, only 16% of the medication is protein bound in the serum, corresponding to a short half-life of 3-hours.⁴¹ It is minimally metabolized in the liver, with more than 95% of the drug being excreted via the kidneys in its original active form.⁴¹ Pharmacodynamically, ceftobiprole is highly potent with low MICs similar to those of carbapenams for all pneumococcal strains and other common CAP organisms, including resistant forms. In fact, it has MICs that are two-fold lower than ceftriaxone for common CAP pathogens.⁴¹

[2.6.2] Clinical Background: It has already completed phase 3 trials, and is currently already approved for use in patients with CAP, hospital-acquired pneumonia (HAP) and soft-tissue infections in over thirteen European countries and several non-European countries including Canada. However it is still waiting for approval from the U.S. FDA.⁴¹ In a randomized, double-blind controlled trial with 666 patients (50% of which were over the age of 65 and had moderate-to-severe pneumonia with PORT scores of III-V), ceftobiprole medocaril was found to be non-inferior to ceftriaxone with or without linezolid for the treatment of patients with CAP requiring hospitalization.⁴² Exclusion criteria consisted mainly of previous antibiotic use. In terms of side-effects, they mainly consisted of nausea (7%) and vomiting (5%).⁴¹ Unfortunately, the US FDA declined to approve ceftobiprole, citing data integrity concerns with two of its supporting studies.⁴¹ Furthermore, inspections and audits of approximately one third of its clinical trial sites found that the data from a large proportion of these sites were unreliable and unverifiable. They requested further long-term phase 3 trials be conducted before regulatory approval.⁴¹

[2.6.3] The NIPS Model: Value to the Elderly: Based on the NIPS model, ceftobiprole has some strengths, however disadvantages exist that weaken its potential role in the elderly population. First, ceftobiprole has a novel mechanism of action and thus is active against many multi-drug resistant organisms. Second, it has minimal reported interactions with other medications, considering it does not interact with the cytochrome P450 isoenzymes and does not bind to an appreciable level with serum proteins. Similarly, it has good tolerability, with low rates of side-effects with the ones that occur mainly mild.⁴¹ Third, it has a strong PD profile owing to its potent bactericidal properties conferred to it by its ability to bind to several different PBPs. However from a PK perspective, it is less favorable because of its poor oral bioavailability. Patients will thus need intravenous access as an outpatient, potentially limiting its role in the outpatient setting. Furthermore, Ceftobiprole has a short half-life requiring three-times-per-day dosing, creating compliance concerns in the elderly population. Overall, ceftobiprole has a low NIPS score. That being said, if further phase 3 trials are able to confirm its safety and efficacy, ceftobiprole may be a potential option despite its frequent dosing interval and lack of oral availability if other antibiotic choices are limited or unavailable.

[2.7] DELAFLOXACIN:

[2.7.1] Pharmacology: In contrast to other fluoroquinolones, this novel and dual targeting fluoroquinolone is capable of forming high affinity inhibitory complexes with both topoisomerase IV and DNA gyrase enzymes within gram positive and negative bacteria, providing it with a broad spectrum of activity and a high degree of potency.^{43, 44} This unique

property arises from its unique binding capacity stemming from specific nucleic acid substitutions providing it with an anionic character at neutral pH with greater accumulation within bacteria at more acidic pH's.^{43, 44} Other fluoroquinolones have far less activity in acidic environments.⁴³ Furthermore, it has a broad spectrum of activity, targeting gram-positives, gram-negatives, atypical and anaerobic organisms.⁴³ It also has activity against resistant organisms such as MRSA and inhibits the production of biofilm production.⁴³ Due to its novel mechanism of action it understandingly has activity against common CAP pathogens resistant to classical fluoroquinolones as well.⁴³ From a PK perspective it is available in both intravenous and oral forms.⁴⁴ It has a bioavailability of 58% when given orally and can be dosed without regard to food.⁴⁴ It is only 16% protein bound, and has a relatively long half-life of approximately 12-hours, requiring only twice per day dosing.⁴⁴ It appears to be mainly metabolized via the kidney with 64% of the drug appearing in the kidney as a metabolite, with the remaining eliminated in its unchanged form via the fecal route.⁴⁵ Pharmacodynamically, it has a high bactericidal potency with two-to-fourfold lower MICs compared to other fluoroquinolones for common CAP pathogens.⁴⁵ It has even lower MICs in acidic environments where the drug has upwards of a tenfold increase in its intracellular accumulation level.⁴⁵

[2.7.2] Clinical Background: Delafloxacin has successfully completed two phase 3 clinical trials, providing evidence as to its efficacy and tolerability in patients with soft tissue infections.⁴⁵ Researchers are currently enrolling patients in Delafloxacin's first phase 3, multicenter, randomized, double-blind, controlled trial comparing its efficacy and safety to moxifloxacin in patients with mild-to-severe CAP with PORT scores of II-V ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02679573) identifier: NCT02679573).⁴⁶ The primary end-point in this trial is early clinical response, with important secondary end-points such as mortality rates.⁴⁶ Exclusion criteria mainly included prior antibiotic use and patients who were currently immunosuppressed.⁴⁶ In terms of reported side effects, they were generally mild and did not lead to the discontinuation of the medication, consisting mainly of diarrhea (10%) and nausea (12%), without any increase in the rates of arrhythmias or prolongation in QTc intervals.⁴⁵ Delafloxacin has been designated a 'Qualified Infectious Disease Product (QIDP) and has been granted fast track status by the FDA for CAP once phase 3 trials are completed. It is currently not yet formally approved by the U.S. FDA, EMA or other regulatory agencies for use in patients with CAP.

[2.7.3] The NIPS Model: Value to the Elderly: Based on the NIPS model, Delafloxacin has a number of valuable strengths. First, it has a novel mechanism of action with activity against multi-drug resistant organisms.⁴⁷ Along these lines, in-vitro studies have shown that the development of resistance to Delafloxacin is difficult since it requires the accumulation of several mutations that collectively affect both its targets (topoisomerase IV and DNA gyrase).⁴⁷ Furthermore, it does not seem to be a good substrate for bacterial efflux pumps.⁴⁷ Second this antibiotic has minimal interactions without metabolism in the cytochrome P450 system or any human hepatic microsomal system.^{45, 47} Its safety and tolerance profile is consequently also favorable, with only minimal amounts of minor side-effects.⁴⁵ Third it has a favorable PK and PD profile, with high potency for common and resistant CAP pathogens, especially in acidic environments.^{44, 45} Its good bioavailability

also allows easy transition from intravenous therapy to continued oral therapy as an outpatient.⁴³ Lastly, it requires only twice per day dosing in both the oral and intravenous routes, making the dosing regimen relatively simplistic.⁴³ Overall, Delafloxacin has a high NIPS model score with a high potential for effective utilization in the elderly population. (Table 2)

[3] CONCLUSION

All the medications reviewed have valuable characteristics to offer for the treatment of CAP in the elderly population. Clinicians will need to weigh their various strengths and weaknesses based on the unique challenges that face the elderly before deciding on the optimal antibiotic choice. Researchers in the area of antibiotic development will be aided by considering the tenants of the San Antonio NIPS model when designing newer generations of antibiotics.

[4] EXPERT OPINION

The elderly population have a unique and often underappreciated set of treatment challenges. A number of newly developed antibiotics were systematically reviewed above, with the goal to weigh their relative strengths and weaknesses for utilization among this patient population. *Nemonaxacin* and *Delafloxacin* were the only antibiotics reviewed that were given high NIPS model scores. They both had many valuable strengths, including a novel mechanism of action allowing them to treat drug-resistant organisms, were well tolerated with minimal medication interactions, were highly potent and had simplistic dosing regimens. *Solithromycin* *Lafamulin* and *Omadacycline* were given moderate NIPS model scores. Solithromycin certainly has positive qualities, however tolerance is a large concern, having a high risk for medication interactions and possible hepatic toxicity. Lafamulin also has potential, but received a moderate score due in part to concerns over medication interactions and consequent intolerance. Similarly, Omadacycline also has potential but was limited by its frequent although minor side-effects that may influence compliance. *Pristinamycin* and *Ceftobiprole* received low NIPS model scores, and thus we recommend their use only when more favorable options are unavailable.

Simply due to a lack of data, there are few review papers and editorials that have addressed the topic of specific antibiotic use for CAP in the elderly. Most guidelines also avoid the topic of specific CAP treatment in the elderly for these same reasons. This review article is unique in that regard, providing a potential paradigm to reorganize our focus on antibiotic choices in the elderly and bring attention to a seldom discussed topic that may potentially become a health-care crisis in the next decade.

As a whole, research in the area antibiotic development for CAP is moving in the right direction, however more directed focus is needed on the segment of the population over the age of 65. With this growing age group and alarming statistics alerting us to their poor clinical outcomes, randomized control trials are increasingly enrolling patients over the age of 65 and upwards to the age of 80. At the moment, the CAP guidelines rightfully do not mention different antibiotic therapy for the elderly, but in the upcoming revisions it will be

important to at least address the key characteristics that clinicians will need to be cognizant of when choosing antibiotics for this patient population. Our NIPS Model may provide a conceptual framework to help direct clinicians when they are determining the optimal antibiotic choice for their elderly patients, as well as help guide and inspire future antibiotic research in this patient population.

Acknowledgments

Funding

This paper was not funded

M I Restrepo's time is partially protected by Award Number K23HL096054 from the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, And Blood Institute or the National Institutes of Health or the Department of Veterans Affairs.

REFERENCES

1. Mandell LA , Wunderink RG , Anzueto A , et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2007;44 Suppl 2:S27–7217278083
2. Niederman MS . Community-acquired pneumonia: the U.S. perspective. *Seminars in respiratory and critical care medicine* 2009; 30:179–18819296418
3. Brar NK , Niederman MS . Management of community-acquired pneumonia: a review and update. *Therapeutic advances in respiratory disease* 2011; 5:61–7820935033
4. Vila-Corcoles A , Ochoa-Gondar O , Rodriguez-Blanco T , et al. Epidemiology of community-acquired pneumonia in older adults: a population-based study. *Respiratory medicine* 2009; 103:309–31618804355
5. Woodhead M , Blasi F , Ewig S , et al. Guidelines for the management of adult lower respiratory tract infections--full version. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2011;17 Suppl 6:E1–59
6. Dewan SK , Zheng SB , Xia SJ , et al. Senescent remodeling of the immune system and its contribution to the predisposition of the elderly to infections. *Chinese medical journal* 2012; 125:3325–333122964331
- 7 **. Faverio P , Aliberti S , Bellelli G , et al. The management of community-acquired pneumonia in the elderly. *European journal of internal medicine* 2014; 25:312–319

This article highlights the special needs of the elderly population and their increased morbidity and mortality when they develop community acquired pneumonia. This article will be of special interest to the readers and will put this current review paper in better perspective.

24360244

- 8 **. Meyer KC . The role of immunity and inflammation in lung senescence and susceptibility to infection in the elderly. *Seminars in respiratory and critical care medicine* 2010; 31:561–574
- The predisposition of the elderly to infection due to a weakened immune response to these insults is a seldom discussed topic. This article brings attention to this topic, highlighting the importance of more aggressive and conscientious care of this patient population.

20941657

- 9 **. Faulkner CM , Cox HL , Williamson JC . Unique aspects of antimicrobial use in older adults. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2005;40:997–1004

This article highlights further the unique challenges of treating infections in the elderly, both from a social-psychological perspective, as well as other biological aspects that relate to the natural process of aging.

15824992

10. Zhanel GG , Hartel E , Adam H , et al. Solithromycin: A Novel Fluoroketolide for the Treatment of Community-Acquired Bacterial Pneumonia. *Drugs* 2016; 76:1737–175727909995
11. Barrera CM , Mykietiuik A , Metev H , et al. Efficacy and safety of oral solithromycin versus oral moxifloxacin for treatment of community-acquired bacterial pneumonia: a global, double-blind, multicentre, randomised, active-controlled, non-inferiority trial (SOLITAIRE-ORAL). *The Lancet Infectious diseases* 2016;16:421–43026852726
12. File TM , Rewerska B , Vucinic-Mihailovic V , et al. SOLITAIRE-IV: A Randomized, Double-Blind, Multicenter Study Comparing the Efficacy and Safety of Intravenous-to-Oral Solithromycin to Intravenous-to-Oral Moxifloxacin for Treatment of Community-Acquired Bacterial Pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2016;63:1007–101627448679
13. Fernandes P , Martens E , Bertrand D , et al. The solithromycin journey-It is all in the chemistry. *Bioorganic & medicinal chemistry* 2016;24:6420–642827595539
14. Cooper EC , Curtis N , Cranswick N , et al. Pristinamycin: old drug, new tricks? *The Journal of antimicrobial chemotherapy* 2014;69:2319–232524891428
15. Koechlin C , Kempf JF , Jehl F , et al. Single oral dose pharmacokinetics of the two main components of pristinamycin in humans. *The Journal of antimicrobial chemotherapy* 1990;25:651–6562112540
16. Tremolieres F , Mayaud C , Mouton Y , et al. [Efficacy and safety of pristinamycin vs amoxicillin in community acquired pneumonia in adults]. *Pathologie-biologie* 2005;53:503–51016181747
17. Sanofi Pharmaceuticals. Study to Compare the Efficacy of Pristinamycin (Pyostacine ®) Versus Amoxicillin in the Treatment of Acute Community Acquired Pneumonia. 2016 Available at: <https://clinicaltrials.gov/ct2/show/NCT02332577>.
18. Leclercq R , Soussy CJ , Weber P , et al. [In vitro activity of the pristinamycin against the isolated staphylococci in the french hospitals in 1999–2000]. *Pathologie-biologie* 2003;51:400–40412948760
19. Qin X , Huang H . Review of nemonoxacin with special focus on clinical development. *Drug design, development and therapy* 2014;8:765–774
20. Guo B , Wu X , Zhang Y , et al. Safety and clinical pharmacokinetics of nemonoxacin, a novel non-fluorinated quinolone, in healthy Chinese volunteers following single and multiple oral doses. *Clinical drug investigation* 2012;32:475–48622650326
21. Shih K-C . Safety and Efficacy Study of TG-873870 (Nemonoxacin) in Diabetic Foot Infections. 2014 Available at: <https://clinicaltrials.gov/ct2/show/NCT00685698>.
22. Cheng S , Wu R , Hsu Z , et al. Efficacy and Safety of Oral Nemonoxacin in Treatment of Community-Acquired Pneumonia: Subgroup Analysis Results in Taiwanese Patients in a Randomized, Double-Blind, Multi-Center, Phase III Comparative Study with Levofloxacin. 2015 Available at: www.atsjournals.org/doi/abs/10.1164/ajrcm-conference.2015.191.1_MeetingAbstracts.A4063.
23. TaiGen Biotechnology. A Phase III Study to Evaluate the Efficacy and Safety of Intravenous Infusion of Nemonoxacin in Treating CAP. 2016 Available at: <https://clinicaltrials.gov/ct2/show/NCT02205112>.
24. van Rensburg DJ , Perng RP , Mitha IH , et al. Efficacy and safety of nemonoxacin versus levofloxacin for community-acquired pneumonia. *Antimicrobial agents and chemotherapy* 2010; 54:4098–410620660689
25. Poole RM . Nemonoxacin: first global approval. *Drugs* 2014; 74:1445–145325079302
26. Sader HS , Paukner S , Ivezic-Schoenfeld Z , et al. Antimicrobial activity of the novel pleuromutilin antibiotic BC-3781 against organisms responsible for community-acquired respiratory tract infections (CARTIs). *The Journal of antimicrobial chemotherapy* 2012; 67:1170–117522287234

27. Rubino CM , Xue B , Bhavnani SM , et al. Population pharmacokinetic analyses for BC-3781 using phase 2 data from patients with acute bacterial skin and skin structure infections. *Antimicrobial agents and chemotherapy* 2015; 59:282–28825348519
28. Prince WT , Ivezic-Schoenfeld Z , Lell C , et al. Phase II clinical study of BC-3781, a pleuromutilin antibiotic, in treatment of patients with acute bacterial skin and skin structure infections. *Antimicrobial agents and chemotherapy* 2013; 57:2087–209423422913
29. Prince W Study Comparing the Safety and Efficacy of Two Doses of BC-3781 vs Vancomycin in Patients With Acute Bacterial Skin and Skin Structure Infection (ABSSSI). 2012 Available at: <https://clinicaltrials.gov/ct2/show/NCT01119105>.
30. Seltzer E Study to Compare Lefamulin to Moxifloxacin (With or Without Linezolid) for the Treatment of Adults With Pneumonia (LEAP). 2016 Available at: <https://clinicaltrials.gov/ct2/show/NCT02559310>.
31. Gasink L Study to Compare Lefamulin to Moxifloxacin for the Treatment of Adults With Pneumonia (LEAP2). 2016 Available at: <https://clinicaltrials.gov/ct2/show/NCT02813694>.
32. Eyal Z , Matzov D , Krupkin M , et al. A novel pleuromutilin antibacterial compound, its binding mode and selectivity mechanism. *Scientific reports* 2016; 6:39004.27958389
33. Paukner S , Riedl R . Pleuromutilins: Potent Drugs for Resistant Bugs-Mode of Action and Resistance. *Cold Spring Harbor perspectives in medicine* 2016; 7: a027110
34. Macone AB , Caruso BK , Leahy RG , et al. In vitro and in vivo antibacterial activities of omadacycline, a novel aminomethylcycline. *Antimicrobial agents and chemotherapy* 2014; 58:1127–113524295985
35. Villano S , Steenbergen J , Loh E . Omadacycline: development of a novel aminomethylcycline antibiotic for treating drug-resistant bacterial infections. *Future microbiology* 2016;11:1421–143427539442
36. Tanaka SK , Villano S . In Vitro and In Vivo Assessments of Cardiovascular Effects with Omadacycline. *Antimicrobial agents and chemotherapy* 2016;60:5247–525327324778
37. Flarakos J , Du Y , Gu H , et al. Clinical disposition, metabolism and in vitro drug-drug interaction properties of omadacycline. *Xenobiotica; the fate of foreign compounds in biological systems* 2016:1–15
38. Paratek Pharmaceuticals. Omadacycline. 2017 Available at: <http://paratekpharma.com/science/omadacycline/>
39. Paratek Pharmaceuticals. Omadacycline vs Moxifloxacin for the Treatment of CABP. 2016 Available at: <https://clinicaltrials.gov/ct2/show/NCT02531438>
40. Kising J , Whitney D . Ceftobiprole, a Broad-Spectrum Cephalosporin With Activity against Methicillin-Resistant *Staphylococcus aureus* (MRSA). *P & T : a peer-reviewed journal for formulary management* 2008;33:631–64119750059
41. Liapikou A , Cilloniz C , Torres A . Ceftobiprole for the treatment of pneumonia: a European perspective. *Drug design, development and therapy* 2015;9:4565–4572
42. Nicholson SC , Welte T , File TM , et al. A randomised, double-blind trial comparing ceftobiprole medocaril with ceftriaxone with or without linezolid for the treatment of patients with community-acquired pneumonia requiring hospitalisation. *International journal of antimicrobial agents* 2012; 39:240–24622230331
43. Van Bambeke F Delafloxacin, a non-zwitterionic fluoroquinolone in Phase III of clinical development: evaluation of its pharmacology, pharmacokinetics, pharmacodynamics and clinical efficacy. *Future microbiology* 2015;10:1111–112326119479
44. Kocsis B , Domokos J , Szabo D . Chemical structure and pharmacokinetics of novel quinolone agents represented by avarofloxacin, delafloxacin, finafloxacin, zabofloxacin and nemonoxacin. *Annals of clinical microbiology and antimicrobials* 2016; 15:3427215369
45. O’Riordan W , Mehra P , Manos P , et al. A randomized phase 2 study comparing two doses of delafloxacin with tigecycline in adults with complicated skin and skin-structure infections. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2015;30:67–7325448332

46. Melinta Therapeutics Inc. Study to Compare Delafloxacin to Moxifloxacin for the Treatment of Adults With Community-Acquired Bacterial Pneumonia (DEFINE-CABP). 2016 Available at: <https://clinicaltrials.gov/ct2/show/NCT02679573>
47. Candel FJ , Penuelas M Delafloxacin: design, development and potential place in therapy. Drug design, development and therapy 2017;11:881–891

ARTICLE HIGHLIGHTS

- Antibiotic choices in the elderly are difficult and complex due to their higher rates of cognitive deficits impacting compliance, age associated immunosuppression, polypharmacy and medication interactions and finally increased rates of antimicrobial resistance to their greater cumulative exposures.
- The San Antonio NIPS model is a novel conceptual framework that can be used to evaluate the potential effectiveness of antimicrobials in the elderly based on their ability to address the unique challenges faced by this vulnerable population.
- Its overarching goal is to reorganize a clinician's focus on antibiotic selection in the elderly, allowing more effective choices that have the potential to impact not only the morbidity and mortality of individual patients, but also health care costs.
- With aid from the San Antonio NIPS model, we present and systematically review 7 novel antibiotics that are currently in advanced stages of development (phase 3 and above) that show promise for the treatment of CAP in those over the age of 65:
 - i. Solithromycin
 - ii. Pristinamycin
 - iii. Nemonaxacin
 - iv. Lefamulin
 - v. Omadacycline
 - vi. Cefetoprole
 - vii. Delafloxacin
- After reviewing the San Antonio NIPS model which incorporates the four key characteristics that the optimal antimicrobial agent should possess in order to adequately treat CAP in the elderly, we evaluate the relative effectiveness of these 7 antibiotics, providing each with a NIPS model score.
- Although all the antibiotics reviewed have valuable characteristics to offer for the treatment of CAP in the elderly population, Nemonaxacin and Delafloxacin were the only agents given a high NIPS score.

Table 1:

The San Antonio NIPS Model

Model Subcomponent	Meaning	Scoring (Point System) *
N	(N) for 'Novel Mechanism of Action'	0: -Without a novel mechanism of action (mechanism comparable to current agents on the market and in active use)
		1 : -Novel mechanism of action
I	(I) for 'Avoidance of Interactions and Intolerance'	0: -Potential for frequent interactions based on pharmacokinetics -Or frequent (>10%) / severe side-effects
		1 : -Minimal interactions and side-effects
P	(P) for 'Favorable Pharmacokinetic and Pharmacodynamic Profiles'	0: -Available only in IV or oral formulations -Low Potency
		1 : -High potency with MIC's significantly lower compared currently available agents (comparable MICs to currently available agents acceptable) -Also available in both oral and IV formulations
S	(S) for 'Simplicity of Dosing'	0: >= 3x/day dosing
		1: 2x/day or daily dosing

* 4-Points: "High NIPS Model Score"

3-Points: "Moderate NIPS Model Score"

2-Points or less: "Low NIPS Model Score"

Table 2:

Summary of the Seven Antibiotics and their Key Comparisons

Antibiotic	Novel Mechanism of Action	Oral and IV Formulations	Frequency of Interactions	Side-Effects	Dosing Frequency	Phase of Study	NIPS Score
Solithromycin	-4 th Generation Macrolide -First fluoroketolide in development -Binds to an additional site on rRNA	-Oral & IV	-High	Major -Potential for severe hepatic toxicity -Further studies needed	-Once daily	-Completed two phase 3 Trials -FDA approval delayed	Moderate
Pristinamycin	-A Combination of a macrolide and a depsipeptide resulting synergism and irreversible binding to its target	-Oral only	-High	Mild -Nausea -Vomiting -Diarrhea	-Three times per day	-Phase 4	Low
Nemonaxacin	-A non-fluorinated quinolone with a methoxy group replacing the fluorine residue at the C-8 position -Unique structure allows it to target both topoisomerase II and IV within bacteria	-Oral & IV	-Minimal	Mild -Nausea -Diarrhea -Headaches	-Once daily	-Completed one phase 3 trial and a second has completed enrollment -Pending FDA approval once 2 nd phase 3 trial is published	High
Lefamulin	-Pleuromutilin class of antibiotics -Binds to the peptidyl transferase component of the 50S subunit of bacterial ribosomes	-Oral & IV	-High	Mild -Diarrhea -Nausea -Diarrhea	-IV: once daily -Oral: twice daily	-Currently enrolling in two phase 3 trials	Moderate
Omadacycline	-Aminomethycycline -A tetracycline-like compound with an altered chemical structure -Able to overcome the efflux and ribosomal protection mechanisms of common CAP pathogens	-Oral & IV available but oral bioavailability is only 35%	-Minimal	Mild but Frequent -Nausea -Headaches -Constipation -Dizziness -Vomiting	Once daily	-Currently enrolling in a phase 3 trial	Moderate
Ceftobiprole	-An extended spectrum beta-lactam that is able to bind to several different penicillin-binding-proteins on bacterial organisms	V	-Minimal	Mild -Nausea -Vomiting	Three times per day dosing	-Completed two phase 3 trials -FDA approval delayed until further phase 3 trials are completed	Low
Delaflaxacin	-Dual targeting fluoroquinolone able to target both topoisomerase IV and DNA gyrase with high affinity -Amplified activity in	-Oral & IV	Minimal	Mild	Twice per day dosing	-Currently enrolling in a phase 3 trial	High

Antibiotic	Novel Mechanism of Action	Oral and IV Formulations	Frequency of Interactions	Side-Effects	Dosing Frequency	Phase of Study	NIPS Score
	acidic environments due to its anionic structure at neutral ph -Inhibits biofilm production						