

Revised Abstract

Background: Bacterial sinusitis affects 1.4 out of every 10 adults resulting in more than 30 million doctor visits annually. Surveillance of antimicrobial susceptibility, particularly oral agents, is necessary for effective therapy. The Tigecycline Evaluation and Surveillance Trial (TEST) program has monitored the activity of antimicrobial agents in patients with sinusitis since 2004.

Methods: 539 investigational sites in United States collected 1,052 sinusitis isolates from 2004-2009. MICs were determined by broth microdilution, and interpreted using current CLSI guidelines. Susceptibility rates for isolates were determined for species with ≥ 10 isolates.

Results: Oral antimicrobial activity against bacterial isolates from sinusitis infections in the US:

Organism (N)	%Susceptible / MIC ₅₀ (µg/ml)						
	A/C	AMP	LEV	MIN	LZ	PEN	AZ
<i>A. baumannii</i> (16)	na>32	na>32	68.8/>8	75/8	na	na	na
<i>E. aerogenes</i> (32)	6.3/>32	9.4/>32	96.9/0.25	78.1/8	na	na	na
<i>E. coli</i> (23)	83.3/16	41.7/>32	70.8/>8	79.2/8	na	na	na
<i>H. influenzae</i> (281)	99.67/1	65.1/>32	100/0.03	na	na	na	na
<i>K. pneumoniae</i> (35)	88.6/16	5.7/>32	82.7/8	91.4/4	na	na	na
<i>P. aeruginosa</i> (81)	na>32	na>32	71.6/8	na/>16	na	na	na
<i>S. aureus</i> , MRSA (101)	0/>8	0/>16	18.3/>32	100/≤0.25	100/4	0/>8	na
<i>S. aureus</i> , MSSA (111)	100/2	18.9/>16	93.7/0.5	100/≤0.25	100/4	16.2/>8	na
<i>S. agalactiae</i> (10)	100/0.12	100/0.12	100/0.5	na	100/1	100/0.12	na
<i>S. pneumoniae</i> (268)	79.5/4	na	99.6/1	na	100/1	44/4	52.3/>64

na = not tested or breakpoints not defined. A/C=amoxicillin/clavulanic acid; AMP=ampicillin; LEV=levofloxacin; MIN=minocycline; LZ=linezolid; PEN=penicillin; AZ=azithromycin.

Conclusions:

- H. influenzae* was the most frequent bacteria isolated from infected sinuses, followed closely by *S. pneumoniae* and *S. aureus*. Both LEV and LZ were highly effective against *S. pneumoniae*. LEV and A/C were most effective against *H. influenzae*.
- S. aureus* was the third most frequently isolated bacteria with MRSA and MSSA occurring in about equal proportions. Although A/C, LEV, MIN and LZ all inhibited >90% of MSSA at their respective breakpoints, only LZ and MIN were 100% effective against both MSSA and MRSA.
- P. aeruginosa* ranked 4th for which LEV was the only available choice in this study (71.6% sus).
- Recommendations based on this study would include empirical therapy with LEV for suspected gram-negative infections when *P. aeruginosa* is not likely, and LZ for suspected gram-positive infections.

Introduction

Bacterial sinusitis is a frequent cause of adult respiratory tract infections and a common illness in primary care. As many as 13% of adults have been told by their physician that they have sinusitis [1]. In 2008, sinusitis resulted in an estimated 30 million doctor's visits. Sinusitis may be difficult to diagnose and treatment is often empirical. The emergence of drug resistance among both gram-negative and gram-positive pathogens often makes the choice of effective therapy challenging.

This study was undertaken to document the most frequently isolated pathogens from sinus infections in the United States and the *in vitro* activity of commonly prescribed oral antibiotics. This study is part of the ongoing global Tigecycline Evaluation and Surveillance Trials (TEST) program.

Materials & Methods

- A total of 1,052 clinical isolates from sinus sources were collected and tested between January 2004 and December 2010 from 539 cumulative sites in the United States. Isolates were identified to the species level and tested at each site by the participating laboratory using supplied dried broth microdilution panels.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [2]. MIC interpretive criteria followed published guidelines established by the CLSI [3], where available.
- Quality controls (QC) were performed by each testing site on each day of testing using appropriate ATCC control strains. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2011) guidelines [3].

References

- Centers for Disease Control. 2008. Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2008. National Center for Health Statistics, Hyattsville, MD. DHHS Publication No. 2020-1570. Series 10, No. 242;1-157.
- Clinical and Laboratory Standards Institute. 2009. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Eighth Edition, CLSI Document M7-A8. Wayne, PA.
- Clinical and Laboratory Standards Institute. 2011. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-first Informational Supplement. CLSI document M100-S21. Wayne, PA.

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Results

Table 1. Ranking of top 12 species isolated from 1,052 sinus infections from sites in the United States, 2004-2009.

Rank	Organism	N	% Total N
1	<i>Haemophilus influenzae</i>	281	26.7%
2	<i>Streptococcus pneumoniae</i>	268	25.5%
3	<i>Staphylococcus aureus</i> , MSSA	111	10.6%
3	<i>Staphylococcus aureus</i> , MRSA	101	9.6%
4	<i>Pseudomonas aeruginosa</i>	81	7.7%
5	<i>Serratia marcescens</i>	40	3.8%
6	<i>Klebsiella pneumoniae</i>	35	3.3%
7	<i>Enterobacter aerogenes</i>	32	3.0%
8	<i>Escherichia coli</i>	24	2.3%
9	<i>Enterobacter cloacae</i>	23	2.2%
10	<i>Klebsiella oxytoca</i>	18	1.7%
11	<i>Acinetobacter baumannii</i>	16	1.5%
12	<i>Streptococcus agalactiae</i>	10	1.0%
	All Others *	12	1.1%
	Grand Total	1,052	100%

* All Others includes: *A. lwoffii* (5), *E. faecalis* (4), *A. junii* (1), *S. liquefaciens* (1), *E. agglomerans* (1)

Figure 1. Distribution of gram-negative and gram-positive species in 1,052 sinus infections in the United States, 2004-2009.

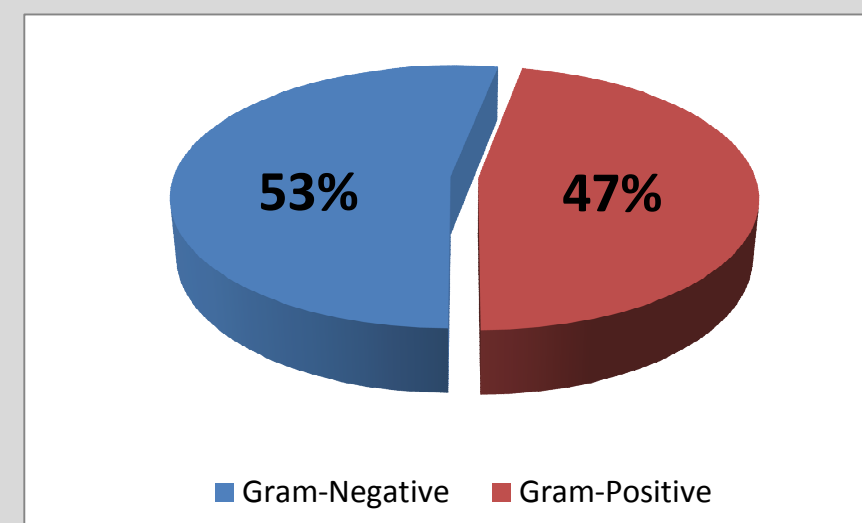


Table 2. *In vitro* activity of oral antibiotics against 550 gram-negative sinus pathogens, 2004-2009.

Organism	Drug ^a	mcg/ml			%Sus	%Int	%Res
		Range	MIC ₅₀	MIC ₉₀			
<i>Acinetobacter baumannii</i> (n=16)	Levofloxacin	0.06 ->8	0.12	>8	68.8	6.3	25
	Minocycline	≤0.5 - 16	≤0.5	8	75	18.8	6.3
<i>Enterobacter aerogenes</i> (n=32)	AmoxClav	2 ->32	>32	>32	6.3	9.4	84.4
	Ampicillin	2 ->32	>32	>32	9.4	3.1	87.5
	Levofloxacin	0.015 - 4	0.06	0.25	96.9	3.1	0
	Minocycline	≤0.5 ->16	2	8	78.1	12.5	9.4
<i>Enterobacter cloacae</i> (n=23)	AmoxClav	4 ->32	>32	>32	8.7	8.7	82.6
	Ampicillin	≤0.5 ->32	>32	>32	8.7	4.4	87
	Levofloxacin	0.015 - 4	0.06	0.12	95.7	4.4	0
	Minocycline	≤0.5 - 8	2	4	95.7	4.4	0
<i>Escherichia coli</i> (n=24)	AmoxClav	2 - 32	8	16	83.3	12.5	4.2
	Ampicillin	1 ->32	>32	>32	41.7	0	58.3
	Levofloxacin	0.015 ->8	0.03	>8	70.8	0	29.2
	Minocycline	≤0.5 - 16	1	8	79.2	16.7	4.2
ESBL-Positive <i>E. coli</i> (n=1)	AmoxClav	16 - 16	-	-	-	-	-
	Ampicillin	>32 ->32	-	-	-	-	-
	Levofloxacin	>8 ->8	-	-	-	-	-
	Minocycline	2 - 2	-	-	-	-	-
<i>Haemophilus influenzae</i> (n=281)	AmoxClav	≤0.12 - 32	0.5	1	99.6	0	0.4
	Ampicillin	≤0.5 ->32	≤0.5	>32	65.1	2.1	32.7
	Levofloxacin	≤0.008 - 0.5	0.015	0.03	100	0	0
Beta-Lactamase-Positive <i>H. influenzae</i> (n=95)	AmoxClav	0.25 - 32	1	2	99	0	1.1
	Ampicillin	2 ->32	32	>32	0	3.2	96.8
	Levofloxacin	≤0.008 - 0.25	0.015	0.03	100	0	0
<i>Klebsiella oxytoca</i> (n=18)	AmoxClav	1 - 16	2	8	94.4	5.6	0
	Ampicillin	16 ->32	>32	>32	0	16.7	83.3
	Levofloxacin	0.015 ->8	0.03	0.12	94.4	0	5.6
	Minocycline	≤0.5 - 16	1	2	94.4	0	5.6
<i>Klebsiella pneumoniae</i> (n=35)	AmoxClav	1 ->32	2	16	88.6	8.6	2.9
	Ampicillin	8 ->32	32	>32	5.7	14.3	80
	Levofloxacin	0.03 ->8	0.06	8	82.9	2.9	14.3
	Minocycline	≤0.5 ->16	1	4	91.4	2.9	5.7
ESBL-Positive <i>K. pneumoniae</i> (n=4)	AmoxClav	2 - 8	-	-	-	-	-
	Ampicillin	>32 ->32	-	-	-	-	-
	Levofloxacin	8 ->8	-	-	-	-	-
	Minocycline	4 - 8	-	-	-	-	-
<i>Pseudomonas aeruginosa</i> (n=81)	Levofloxacin	0.06 ->8	1	8	71.6	11.1	17.3
	AmoxClav	16 ->32	>32	>32	0	2.5	97.5
<i>Serratia marcescens</i> (n=40)	AmoxClav	16 ->32	>32	>32	0	10	90
	Ampicillin	16 ->32	>32	>32	0	10	90
	Levofloxacin	0.03 - 8	0.12	1	97.5	0	2.5
	Minocycline	1 ->16	2	8	80	15	5

^a Breakpoints defined in CLSI document M100-S21 (2011), where available. Antibiotics without species specific breakpoints were omitted. - MIC₅₀, MIC₉₀ and susceptibilities are not calculated for n's <10.

Conclusions

- Bacterial pathogens in this study were almost evenly divided between gram-negative (53%) and gram-positive (47%) organisms. *H. influenzae* and *S. pneumoniae* were the most frequently isolated bacteria from infected sinuses, accounting for slightly more than 50% of all recovered pathogens. *S. aureus* accounted for another 20% (MRSA 10.6%; MSSA 9.6%).
- Linezolid was the most active antibiotic against the gram-positive pathogens, inhibiting 100% of all isolates at its CLSI susceptible breakpoints of 4 mcg/ml (staph) and 2 mcg/ml (strep). Although amoxicillin-clavulanic acid, levofloxacin, minocycline, and linezolid all inhibited >90% of MSSA at their respective breakpoints, only linezolid and minocycline were 100% effective against both MSSA and MRSA, making empirical choices a challenge for the physician.
- P. aeruginosa* was the most commonly isolated gram-negative organism and fourth most frequent overall. Levofloxacin was the only available oral agent in this study with breakpoints for *P. aeruginosa* (71.6% susceptible).
- Recommendations based on this study would include empirical therapy with levofloxacin for suspected gram-negative infections and linezolid for suspected gram-positive infections.