Comparing Audiometric Threshold Shift Definitions for Ototoxicity Detection

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Outline

- Learning Objectives
- Background
- Study Objectives
- Methods
- Results
- Conclusions & Clinical Implications
- Questions & Answers

Learning Objectives

- Describe rationale for early detection of ototoxic hearing loss
- Outline benefits of using Clinical Decision Theory for examining test performance
- Discuss implications of this study for various ototoxicity monitoring methods
  - Criteria for hearing threshold shifts
  - Test-frequency step sizes
  - Testing above 8 kHz

Background

- Patients may not notice hearing change until speech frequencies affected
- Serum levels are not good indicators cochleototoxicity
- The only way to know if a person is losing their hearing is direct assessment of auditory function

Attributes of Screening Test

- High sensitivity (sensitivity rate=hit rate)
  - High hit rate in exposed ears
- High specificity (1-specificity=false positive rate)
  - Low false alarm rate in unexposed ears
- Most tests are imperfect, so that some clinical errors are made. There is a trade off between sensitivity and specificity
  - Make cutoff more stringent, reduce false positives, but also reduce hit rate
  - Make cutoff more lax, increases hit rate, but also increases false positives
- Time efficiency

Ototoxicity Monitoring

"Now just relax and we'll begin your hearing test."

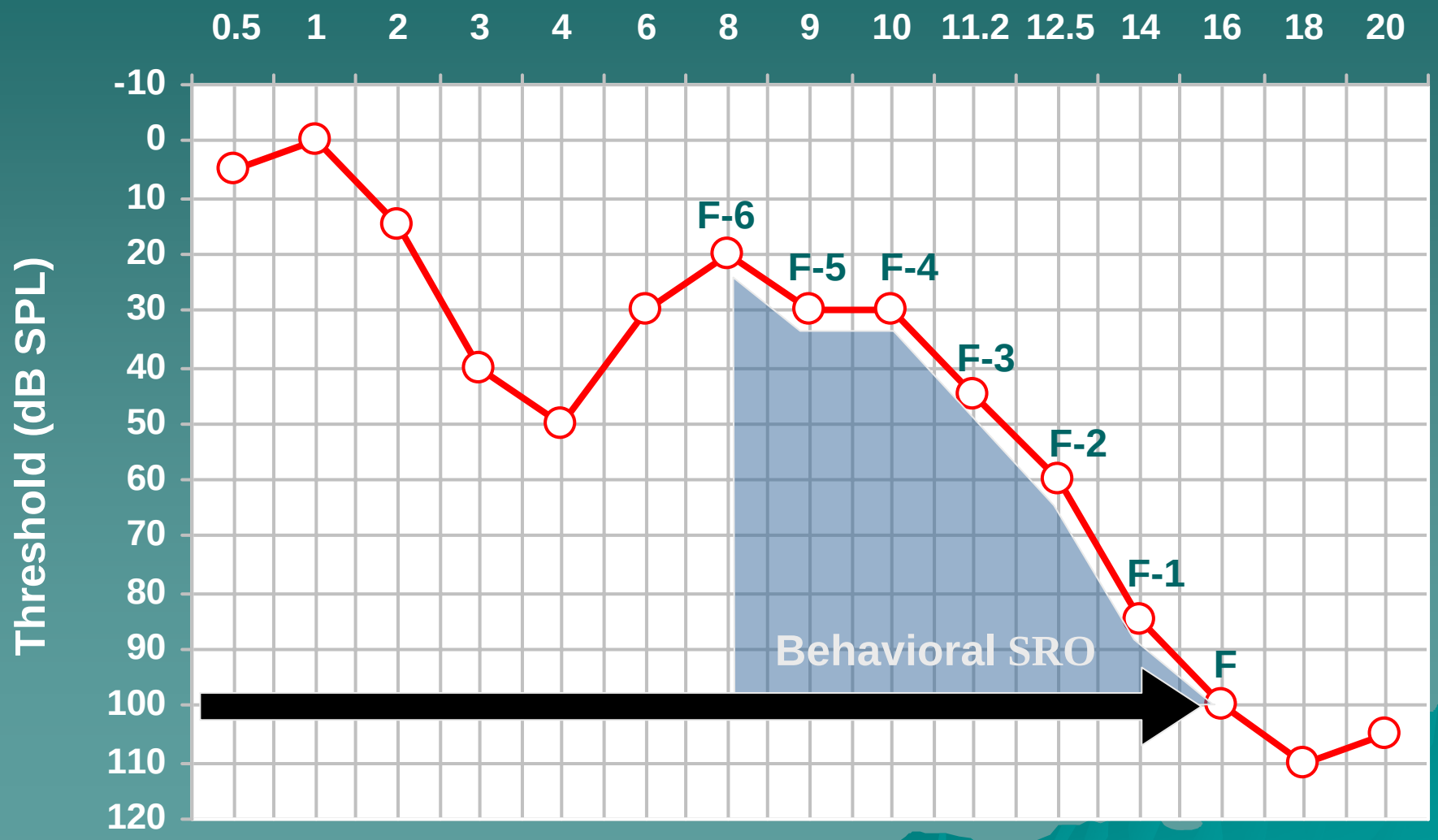
Benefits of Ototoxicity Monitoring

- Early detection may prevent hearing damage that requires rehabilitation
- If change observed, treatment modification can prevent further hearing loss; if no change observed, continued treatment warranted
- Ototoxicity monitoring program
  - educates patients, care givers and physicians about ototoxic symptoms (hearing loss, tinnitus, and balance problems)
  - raises awareness of synergistic effects of toxins and noise
  - ensures audiology work up and rehabilitation plan are implemented if and when appropriate

Sensitive Range of Ototoxicity (SRO) Principle

- Most initial changes seen in a limited range near the highest audible frequency
- Range for each individual is unique and specific to their hearing configuration
- Frequencies with thresholds > 100 dB SPL usually remain unchanged
- A sensitive range for ototoxicity (SRO) can be defined as a one octave range near the upper-frequency limit of hearing (i.e., frequency with a threshold $\leq$100 dB SPL)

Example SRO


0.5
1
2
3
4
6
8
9
10
11.2
12.5
14
16
18
20
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
Threshold (dB SPL)
F-6
F-5
F-4
F-3
F-2
F-1
F
Behavioral SRO

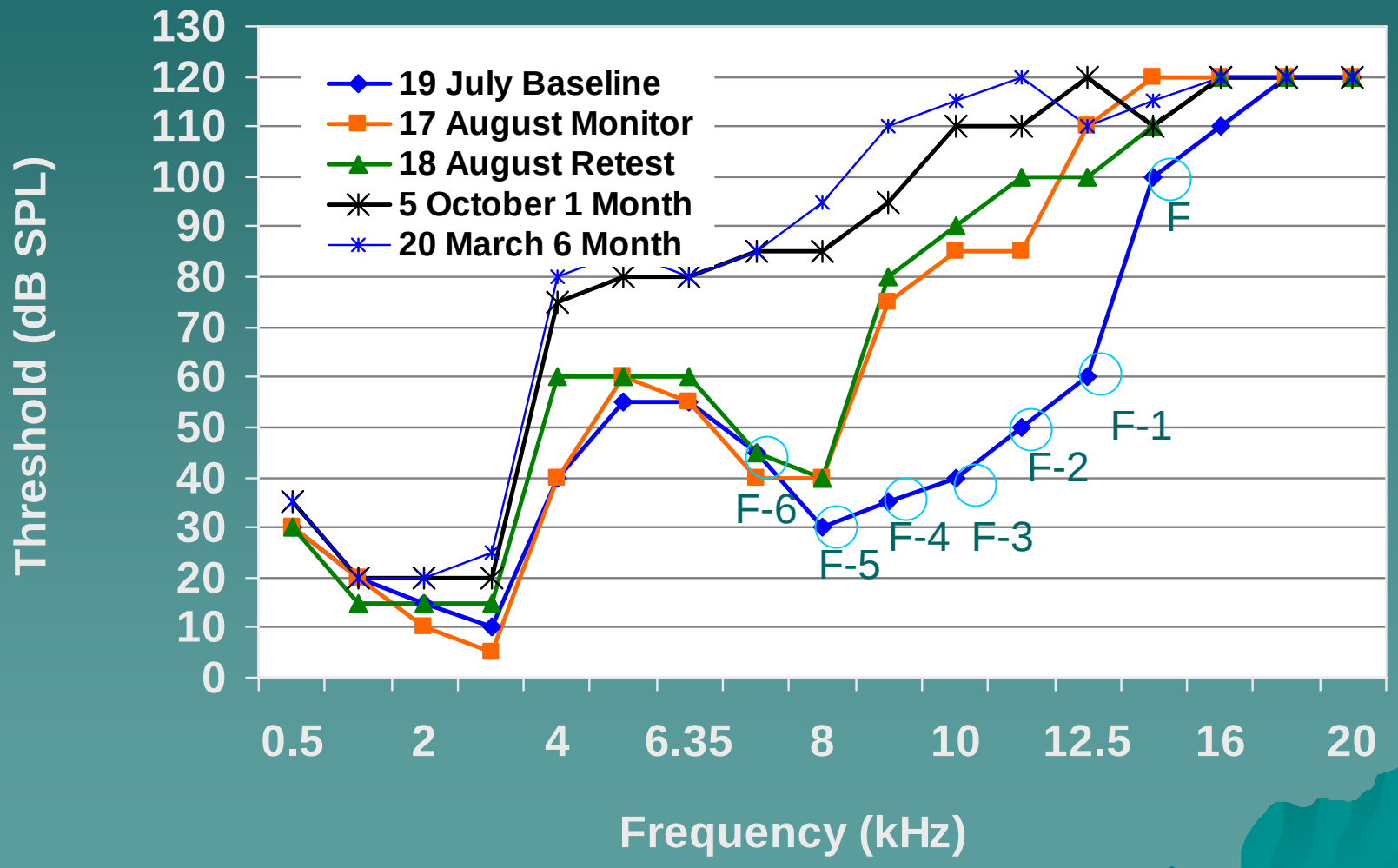
Sensitivity: SRO 1/6th Octave

	Total (Ears)	Hit	Miss	Initial Change in SRO
AMG	54	46	8	85%
Cisplatin	226	207	19	92%
Carboplatin	59	50	9	85%
Total	339	303	36	89%

Ototoxicity Monitoring

- Few studies have compared audiometric methods and hearing loss change criteria
- Methods vary for monitoring hearing in patients receiving ototoxic drugs
  - frequencies tested
  - frequency step sizes used
  - decision variables (number frequencies affected)
  - magnitude of threshold shifts

Case Study: SRO 7.13 - 14 kHz



Case Study

- Conventional audiometric testing (<8 kHz) would have identified hearing change later
- Hearing continued to decline after treatment ended (black line: 1 month post-drug; and light blue line: 6 month post-drug)
  - ultimately, 20-dB change at 3 kHz; 40-dB change at 4 kHz; 65-dB change at 8 kHz
- Greatest changes at the conventional frequencies occurred after treatment ended!
- Information used to council patient about aural rehab options and necessity of follow up with audiologist

Background

- Challenge is to quantify ototoxic changes in a group of adults
- Different frequencies may be affected in a given person, so averaging across all frequencies tested tends to wash out ototoxic changes
- 90% of changes occur within an octave of highest audible frequency (Fausti et al., 1993)
- Therefore, can average threshold shifts across individuals, normalizing to the highest frequency able to be heard

Study Objectives

1. Examine ability of individually-tailored threshold monitoring to detect ototoxic hearing loss using various (significant threshold shift) STS definitions
2. Determine whether evidence supports use of ASHA-recommended STS definitions
3. Determine whether testing in 1/3- or 1/6-octave steps improves test performance when compared to use of 1/2-octave steps

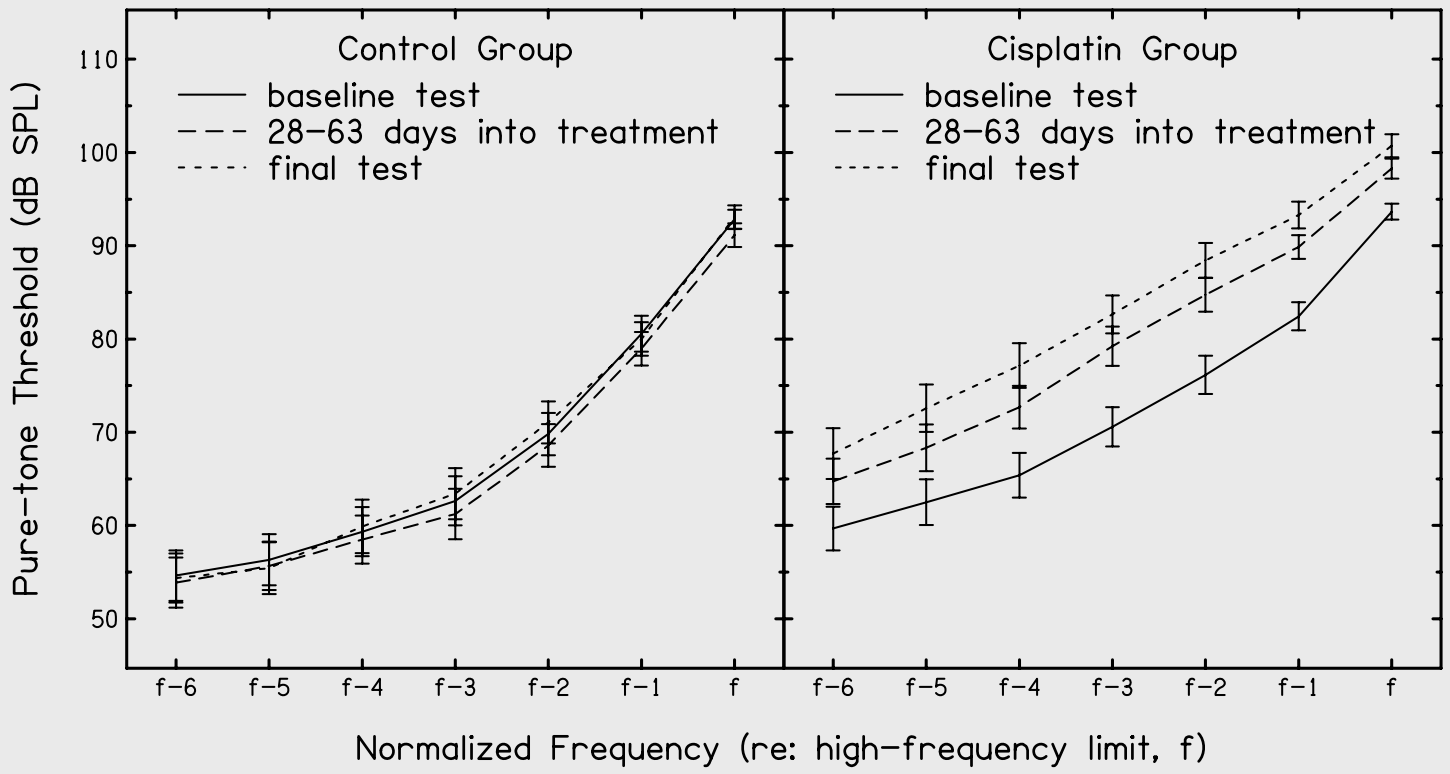
Methods

- All subjects
  - at least 3 audiograms, one audio ~1.5 months, one audio ~6.5 months after initial dose
  - baseline within 2 days of first dose (some controls were within 3 days)
- Cisplatin-exposed Group
  - used for hit or true positive (TP) rates
  - 78 ears of 41 patients receiving cisplatin
  - cumulative dose at least 350 mg
  - mean age 59.4 years (SD 10.2)
- Control Group
  - used for false positive (FP) rates
  - 53 ears of 28 hospitalized patients receiving non-ototoxic antibiotics
  - mean age 56.0 (SD 10.5)

Example: Frequencies Tested in One Subject

Baseline Test Frequencies (kHz)	0.50	1.00	2.00	3.00	4.00	6.00	6.35	7.13	8.00	9.00	10.00	11.20	12.50	14.00	16.00	18.00	20.00
Baseline Hearing Thresholds	25	25	35	40	55	55	55	60	70	75	85	90	100	110	> 115	> 115	> 115
Comparison Test Frequencies *1/6-octave*							F-6	F-5	F-4	F-3	F-2	F-1	F				
Comparison Test Frequencies *1/3-octave*							F-3		F-2		F-1		F				
Comparison Test Frequencies *1/2-octave*							F-2			F-1			F				

Group Data in 1/6th-octaves



Mean data underestimate effect because some subjects have hearing loss at a given frequency, but others do not

Methods

- Hearing changes calculated for frequencies within an octave of high-frequency hearing limit
- Compared initial audiogram to tests obtained 1.5 and 6.7 months later
- Determined if changes met STS criteria
  - based on magnitudes of positive threshold shifts (worsening of thresholds by 5, 10, 15, or 20 dB)
  - and numbers of frequencies affected (threshold shifts at a minimum of 1, 2, or 3 adjacent frequencies)
- Test performance evaluated using CDT

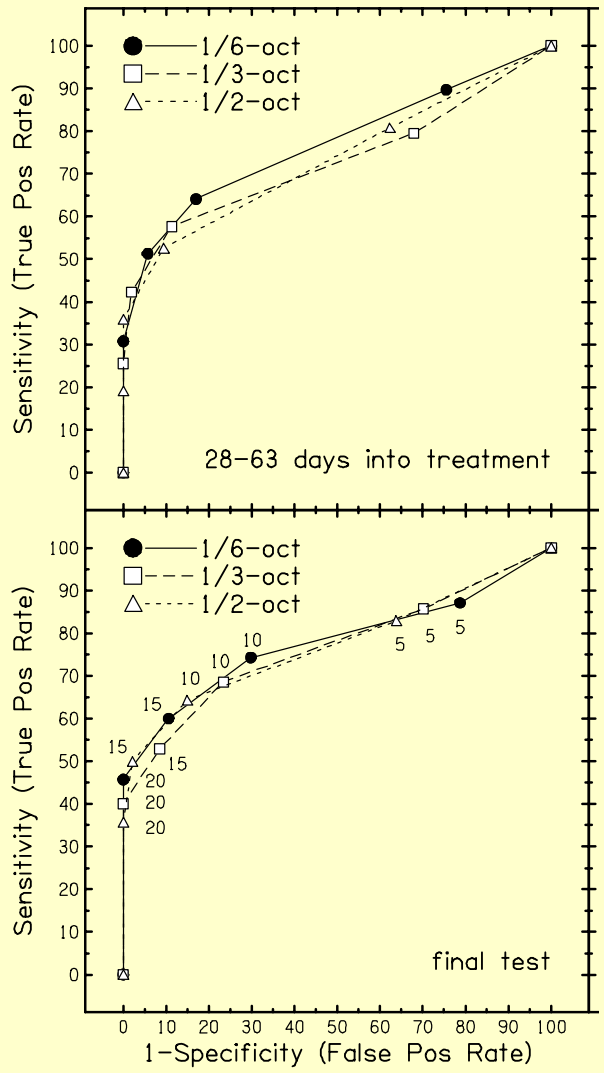
Clinical Decision Theory (CDT)

- Can go beyond asking 'Does the test work or not?', to the more useful question, 'How well does it work in this context?'
- Can estimate test performance for all values of the experimental variable, in this case dB of hearing change
  - in this case 5, 10, 15, or 20 dB of threshold shift
- Can compare various different decision variables
  - in this case, numbers of frequencies affected (1, 2, 3 or more adjacent)
- Note absence of true "gold standard"
- Compared STS rates for cisplatin-exposed group ("true" positive rates) to non-exposed group (false positive rates) following Dobie 2005
  - Underestimates true positive rates
  - Accurately estimates false positive rates
  - Accurately estimates rankings of competing STS criteria

Methods

- Compared test performance 2 ways
- 1. Examined receiver operating characteristic (ROC) curves
  - Plots of true positive rate or sensitivity as a function of false positive rate or 1 minus specificity
  - Compared relative position of curves and areas under the curves
- 2. Determined STS definitions with the highest true positive rates for a fixed false positive rate near 5%
  - Chosen to minimize the number of patients incorrectly diagnosed with ototoxic hearing loss

ROC Curves



Receiver Operating Characteristic (ROC) Curves

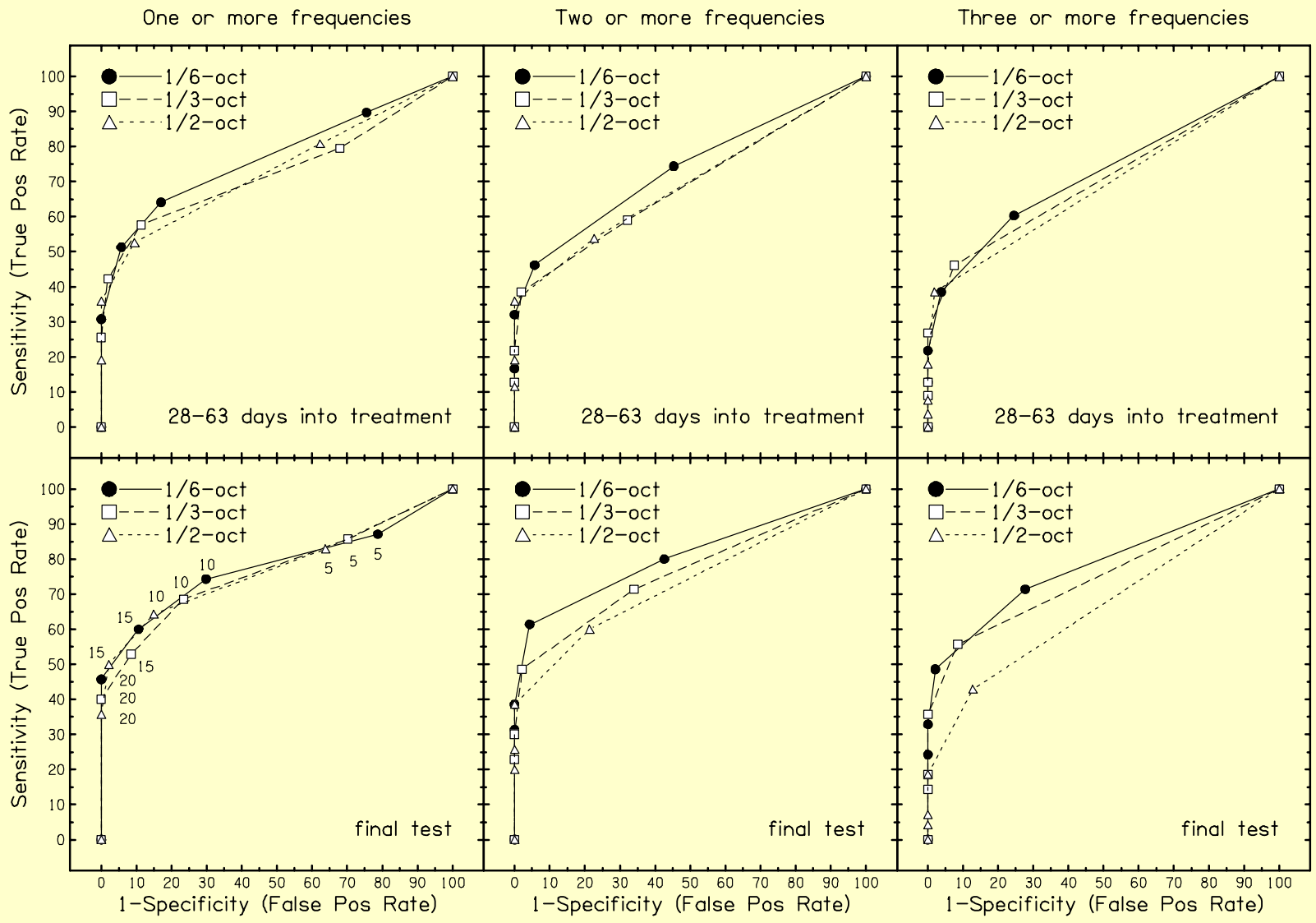
Each point in ROC curve represents a particular criterion cutoff (dB shift)

Sensitivity (true positive rate) is plotted vs false positive rate

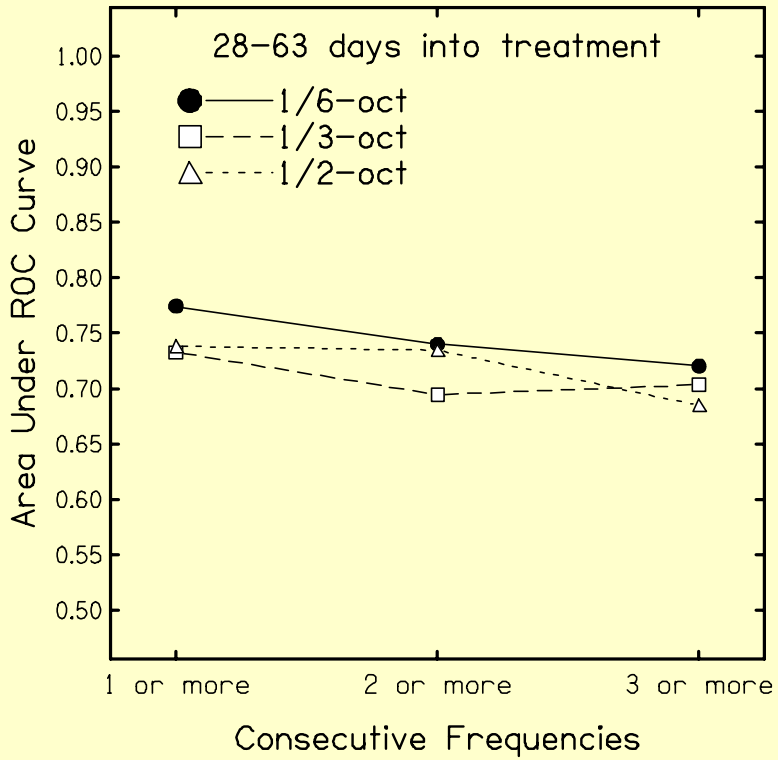
Criterion cutoffs range from stringent (20-dB change) to lax (5-dB change) as curve progresses from left to right

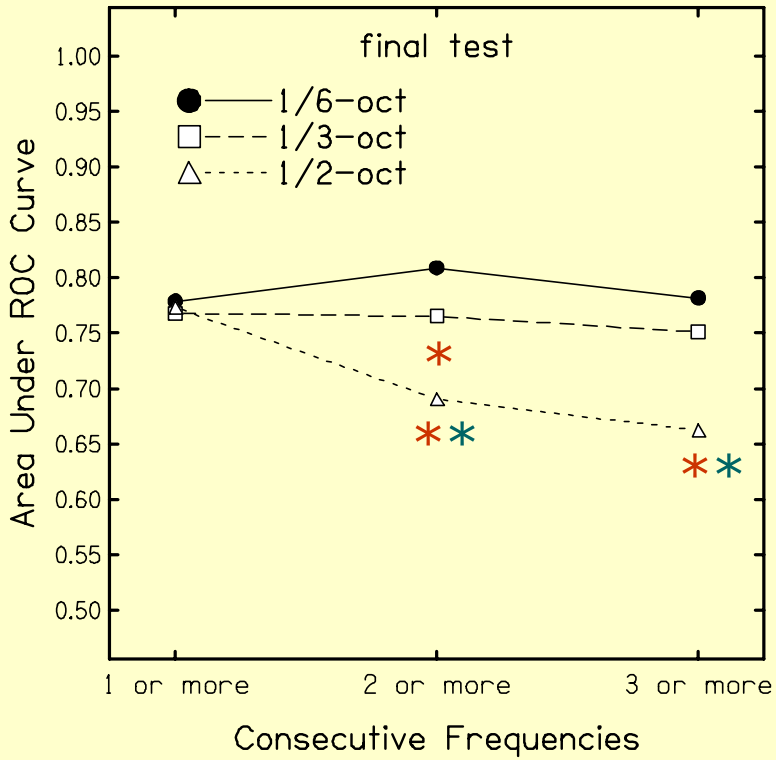
Relative position of curves and area beneath them is used to compare them

ROC Curves

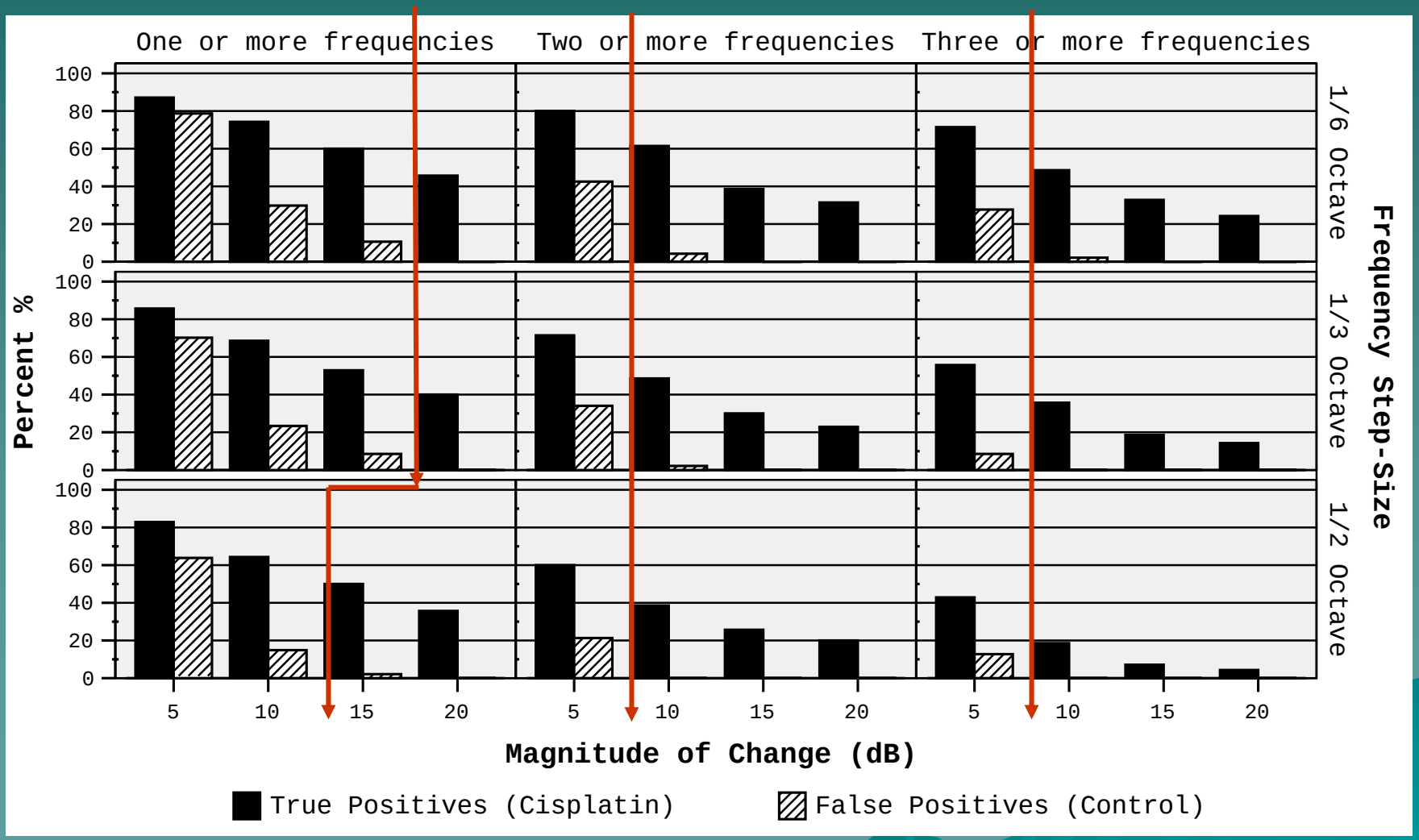

One or more frequencies
Two or more frequencies
Three or more frequencies
1/6-oct
1/3-oct
1/2-oct
28-63 days into treatment
final test
Sensitivity (True Pos Rate)
1-Specificity (False Pos Rate)
0
10
20
30
40
50
60
70
80
90
100
5
10
15
20

AUCs


28–63 days into treatment
1/6–oct
1/3–oct
1/2–oct
Area Under ROC Curve
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
1 or more
2 or more
3 or more
Consecutive Frequencies


final test
1/6–oct
1/3–oct
1/2–oct
Area Under ROC Curve
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
1 or more
2 or more
3 or more
Consecutive Frequencies

Final Test


One or more frequencies
Two or more frequencies
Three or more frequencies
Percent %
100
80
60
40
20
0
1/6 Octave
1/3 Octave
1/2 Octave
Frequency Step-Size
5
10
15
20
Magnitude of Change (dB)
True Positives (Cisplatin)
False Positives (Control)

ASHA Criteria for Hearing Change

- 20 dB change at any 1 test frequency
- 10 dB change at any 2 adjacent test frequencies
- Loss of responses (as little as 5 dB change) at 3 consecutive frequencies, where responses were previously obtained close to the limit of the audiometer
- Changes confirmed by repeat testing

Results

- For the 1/2-octave step size used clinically, best performance was achieved for threshold losses of 15 dB at a single frequency, a change present in 50% of ears by completion of cisplatin therapy.
- Use of smaller frequency step sizes consistently increased test performance; (improvements were significant when threshold shifts were required to occur at 2 or 3 adjacent frequencies)
- Best overall test performance was obtained using 1/6-octave steps and a criterion cut-off of 10 dB at 2 or more frequencies

Results

- Certain ASHA-recommended criteria performed well
  - threshold shifts > 20 dB at 1 frequency
  - > 10-dB at 2 or more adjacent frequencies)
- For ½-octave step size, these STS definitions resulted in TP rates of 36% and 39%, respectively, at the final test date.
- 5-dB at three frequencies performed less well due to increased FP rate

Conclusions & Clinical Implications

- Monitoring protocol that uses a tailored, patient-specific one octave range of frequencies is a clinically effective protocol for detecting early ototoxic changes with an acceptable false positive rate.
- In general, using smaller frequency step sizes increases false positives only slightly, while increasing sensitivity significantly.

High Frequency Audiometers

- Interacoustics AC40
  - High-frequency to 20 kHz, multi-frequency, 1/6 octave (1 octave up to 1/24)
  - With boost feature, 115-120 dB output
  - HL ≤ 8 kHz; SPL > 8 kHz
  - Approximately $6200.

  Decos Systems Audiology Workstation

  High-frequency to 20 kHz, multi-frequency, 1/6 octave

  120 dB HL output at all frequencies-Computer based

  Programmable option for testing in HL & SPL at all frequencies

  Approximately $12,800.

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