



Infektionen in der Pädiatrie

➔ Invasive Pneumokokken-Infektionen

➔ Akute Otitis media

➔ Antimikrobielle Therapie im Kindesalter



Invasive Pneumokokken-Infektionen

Invasive Pneumokokkeninfektionen (IPI)

Hintergrund

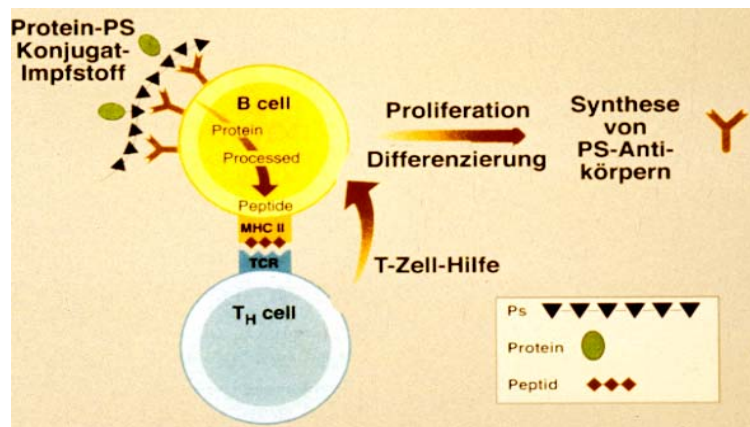
- *Streptococcus pneumoniae* ist weltweit einer der häufigsten Erreger von schweren invasiven Infektionen (IPI).
- Risiko für Infektion altersabhängig mit höchster Inzidenz in ersten 2 Lebensjahren
- Zweiter Inzidenzgipfel ab dem 60. Lebensjahr
- Klinik:
 - ▶ Ambulant erworbene Pneumonie (häufigster Erreger)
 - ▶ Sinusitis, Otitis media
 - ▶ Meningitis
- Analyse Deutschland 1997-2002 (Reinert et al. *Intern J Med Microbiol* 2004):
 - ▶ Letalität der IPI bei Kindern: 4,9%
 - ▶ Langzeitschäden bei Kindern: 12,9%
- Impfung empfohlen für Kinder sowie für Erwachsene ab 60 Jahren

Alter	IPI / 100.000 pro Jahr
0-5 Monate	17,3
6-11 Monate	29,4
1 Jahr	16,3
2-4 Jahre	5,4
5-15 Jahre	1,1
< 5 Jahre	11,1

Verfügbare Impfstoffe: Charakteristika

7-valenter Konjugatimpfstoff

- 7 Serotypen: 4, 6B, 9V, 14, 18C, 19F und 23F
- Konjugat aus Polysaccharid mit Protein
- B- und T-Zell Antwort
- Memory-Effekt
- Hochavide Antikörper
- Mukosale Immunität



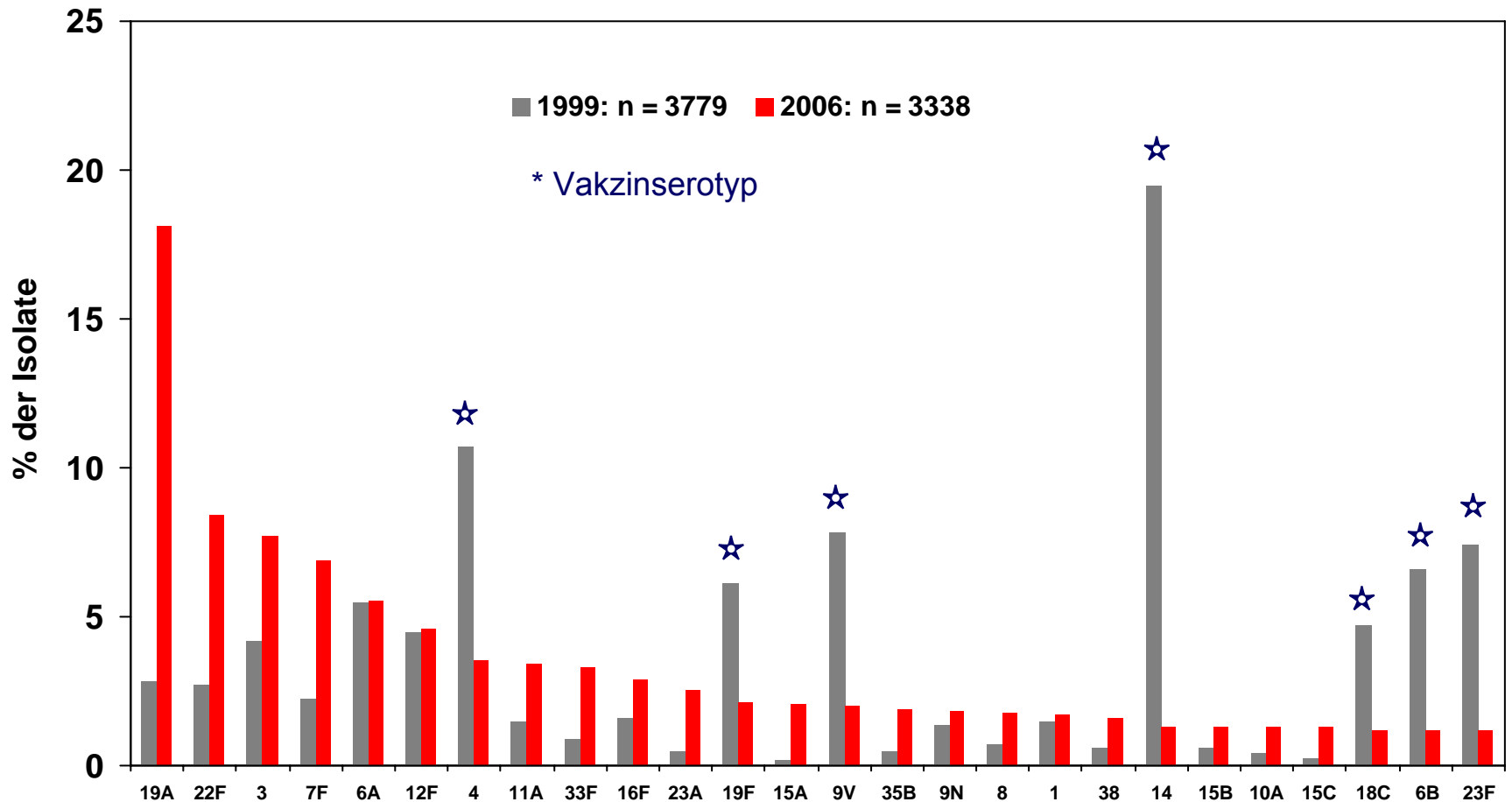
23-valenter Polysaccharidimpfstoff

- 23 Serotypen: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F
- Nicht konjugiert
- Nur B-Zell Antwort
- Kein Memory-Effekt
- Keine hochaviden IgG-Antikörper
- *Keine mukosale Immunität*
- *Ungeeignet für unreifes Immunsystem (z.B. für Kinder)*

Unerwünschter Effekt der Impfung: *Replacement*

- In den USA, wo der Impfstoff PCV7 zuerst eingeführt wurde, kam es anfänglich zu einer kontinuierlichen Abnahme der IPI-Rate; dieser Effekt stagnierte aber überraschenderweise nach einigen Jahren.
- Während die Vakzinserotypen nahezu vollständig eradiziert sind, werden die weiter auftretenden IPI durch Nicht-Vakzin-Serotypen hervorgerufen (*Replacement*).
- Am wichtigsten ist hier der Serotyp 19A, der vor der Einführung der Impfung selten war, jetzt aber zunehmend häufiger beobachtet wird.

Pneumokokkenserotypen in den USA vor und nach Einführung von PCV7 (alle Altersgruppen)



PCV7-Pneumokokkenimpfung: Erfahrung in Dallas, USA

Analysezeitraum 1999-2007

- Impfprogramm seit 2000
- Inzidenz der IPI bei Kindern
 - ▶ 1999 93,6 / 100.000
 - ▶ 2003 41,0 / 100.000
 - ▶ 2005 64,2 / 100.000
 - ▶ 2007 60,0 / 100.000
- Praktisch keine Infektionen durch die von PCV7 abgedeckten Erreger mehr
- Signifikante Häufung von Infektionen durch Serotyp 19A
- 2007 war keiner der 19A-Serotypen Penicillin empfindlich.

PCV7-Pneumokokkenimpfung: Erfahrung in Quebec, Kanada

Surveillance-Programm 1999-2007

- Impfprogramm seit 2004
- Inzidenz der IPI pro 100.000 Personen
 - ▶ 1999-2001 10,9 / 100.000
 - ▶ 2006 8,6 / 100.000
 - ▶ 2007 9,8 / 100.000
- Primäre Abnahme der IPI-Rate durch Rückgang der von PCV7 erfassten Serotypen
- Nachfolgender Anstieg v.a. durch unzureichend oder nicht von PCV7 erfasste Serotypen (19A, 12F, 33A, 7F); besonders auffällig bei Kindern < 2 Jahre

PCV7-Pneumokokkenimpfung: Erfahrung in Deutschland

Surveillance-Programm 2004-2008

- Impfprogramm für Kinder bis 24 Monate seit 1/2007
- *Surveillance* erfasst IPI bei Kindern bis 15 Jahre
- Reduktion von IPI mit PCV7-Serotypen
 - ▶ Kinder 0-23 Monate: um 50%
 - ▶ 69 Fälle (6/2006 bis 3/2007) → 34 Fälle (7/2007 bis 3/2008)
 - ▶ Kinder 2-5 Jahre: nur diskrete Reduktion
- Deutlichste Reduktion für Serotypen 14 und 23F (beide Altersgruppen)
- Jedoch Anstieg der nicht von PCV7 erfassten Serotypen

PCV7-Pneumokokkenimpfung: Internationale Erfahrungen

Kommentar

- In allen Analysen wird nach der Einführung der Impfung gegen Pneumokokken eine Abnahme der Inzidenz der invasiver Pneumokokkeninfektionen beobachtet (durch direkten Impfschutz und Herdenimmunität).
- In der Folgezeit kommt es jedoch zu einem Anstieg der nicht durch die Impfung erfassten Serotypen. Dies ist auch für Deutschland in einigen Jahren zu erwarten.
- Weiteres Vorgehen?
- Neue Impfstrategien?

13-valenter Pneumokokkenimpfstoff

Entwicklung und Testung eines 13-valenten Impfstoffes (PCV13)

- Erfasst außer den PCV7-Serotypen zusätzlich 1, 3, 5, 6A, 7F und 19A
- Aufgrund von Analysen wird erwartet, dass PCV13 in Europa 89% und in den USA 92% der Serotypen erfasst.

Phase-III-Studie zu Sicherheit, Verträglichkeit und Immunogenität

- Impfung von 269 Kindern im Alter von 2, 3 und 4 Monaten

Ergebnisse

- Die Daten zeigen keine Unterschiede zwischen der Vakzine, die in den Pilotstudien verwendet wurde, und der für den kommerziellen Gebrauch hergestellten.
- Gute Verträglichkeit mit normalerweise milden bis mäßigen Nebenwirkungen (Schmerzen, Rötung)
- 1 Kind mit schwerer Nebenwirkung (lang anhaltendes, heftigstes Schreien)
- Gute Antikörperbildung (ELISA) gegen alle im Impfstoff enthaltenen Serotypen
- Ergebnisse funktioneller Tests (*Opsono-Phagozytose-Assay*) unterstützen die Daten der Antikörperbildung

13-valenter Pneumokokkenimpfstoff

Randomisierte Studie

- Vergleich der Sicherheit und Immunogenität von PCV 7 vs. PCV13 bei 303 vs. 301 Kindern

Ergebnisse

- Kein signifikanter Unterschied zwischen beiden Impfstoffen hinsichtlich Sicherheit und Verträglichkeit
- Keine Unterlegenheit von PCV13 gegenüber PCV7 hinsichtlich Antikörperbildung und funktionellen Tests gegen die 7 von beiden Impfstoffen erfassten Serotypen
- Gute Antikörperbildung und funktionelle Aktivität von PCV13 gegenüber den neu erfassten Serotypen (insbesondere 19A!)
- Kein Unterschied in der Impfantwort der normalerweise gleichzeitig verabreichten hexavalenten Impfung (gegen HiB, Diphtherie, HBV etc.)

13-valenter Pneumokokkenimpfstoff

Kommentar

- Die 13-valente Impfung ist viel versprechend hinsichtlich Verträglichkeit und Immunogenität.
- Wichtig sind zukünftige klinische Daten zur Reduktion der IPI, zum Erregershift und zu Resistenzentwicklungen.
- Der 13-valente Impfstoff wird voraussichtlich 2009 zugelassen.
- Erwachsene sollen ebenfalls mit diesem Impfstoff geimpft werden.



Akute Otitis media

Akute Otitis Media (AOM)

Häufigkeit

- Eine der häufigsten Infektionskrankheiten in der pädiatrischen Praxis
- 65-95% aller Kinder erkranken in den ersten Lebensjahren mindestens einmal an einer AOM, 30% sogar mindestens dreimal
- Diagnose durch Klinik und Otoskopie

Erregerspektrum

- Mischinfektionen nicht ungewöhnlich
- Je 50% *S. pneumoniae*, *H. influenzae*
- Je 20% *M. catarrhalis*, *S. pyogenes*, *S. aureus*
- Alleinige Virusinfektionen 10-15%
- Bei ca. 25% der Patienten kein Erreger nachweisbar

Therapie

- Selbstheilungsrate etwa 60%
 - ▶ Diskussion um Notwendigkeit der primären Therapie (symptomatisch, antibiotisch)
 - ▶ Allerdings: langwierige Verläufe und Komplikationen nicht ungewöhnlich
- Dauer der Therapie umstritten (5-10 Tage)
 - ▶ Allerdings: Compliance großes Problem
 - ▶ Deswegen in der Praxis oft verkürzte Therapie

Akute Otitis Media: Prädiktoren des Therapienasprechens

Hintergrund

- Zum Zeitpunkt der Diagnose bisher keine Differenzierung der Kinder mit unproblematischem Verlauf vs. schwieriger Behandlung/Therapieversagen möglich

Studie

- Testung eines klinischen *Scoring*-Systems bei Diagnose einer AOM
 - ▶ *Scoring*-System bestehend aus 10 bzw. 30 Punkten (u.a. Fieberhöhe, Schmerzskala, Trommelfellinspektion)
 - ▶ 327 Kinder (mittleres Alter 13 Monate); 256 Kinder mit problemlosem Verlauf, 71 Therapieversager

Ergebnisse

- ▶ Ergebnis: Gute Korrelation von Score und Verlauf ($r = 0,72$; $p < 0,001$)

Akute Otitis Media: Prädiktoren des Therapienansprechens

Prospektive Analyse

- Mikrobiologisches Ergebnisse bei Kindern mit unkomplizierter AOM (I) vs. Kindern mit Rezidiven (II)
- Patienten: 152 Kinder < 2 Jahre mit AOM, alle mit Pneumokokkenimpfung
- 88 Kinder Gruppe I, 64 Gruppe II

Ergebnis

- Kein Unterschied der nachgewiesenen Erreger zwischen beiden Gruppen: Pneumokokken (23/25%), *H. influenzae* (31/38%), *M. catarrhalis* (9/5%)

Kommentar

- Die wichtige Frage, ob der Verlauf einer AOM bereits bei Diagnose vorhergesagt werden kann, wurde nicht zufriedenstellend beantwortet.
- Das *Scoring*-System erscheint zu kompliziert für die breite Anwendung.
- Die mikrobiologische Untersuchung zeigte keine Unterschiede zwischen Patienten mit komplikationslosem Verlauf und schwieriger Behandlung, wobei keine Resistenzdaten vorliegen.
- Die Ergebnisse legen nahe, dass Wirtsfaktoren die entscheidende Rolle spielen.

Akute Otitis Media: Erregernachweis

Hintergrund

- Soll ein Erregernachweis bei AOM angestrebt werden? Und wenn ja, mit welchen Methoden?
- USA: meist Erregernachweis mittels Parazentese/Punktion zur gezielten antibakteriellen Behandlung angestrebt
- Deutschland: normalerweise keine invasive Diagnostik zum Erregernachweis

Studie

- Sensitivität einer Multiplex-PCR vs. kultureller Methoden
- PCR bei Kindern mit sterilen Kulturen aus dem Mittelohr (Pneumokokken und *Haemophilus influenzae*); der Nasenabstrich war jeweils hinsichtlich der untersuchten Erreger positiv.

Ergebnisse

- In 16/18 sterilen Proben Nachweis von Pneumokokken-DNA
- In 9/12 sterilen Proben Nachweis von *Haemophilus*-DNA
- Die Autoren schlussfolgern, dass die PCR die Sensitivität des Erregernachweises gerade bei Fällen mit sterilen Kulturen beträchtlich erhöhen kann.

Akute Otitis Media: Erregernachweis

Prospektive Analyse

- Therapieansprechen bei Patienten mit versus ohne Erregernachweis in initialen Kulturen
- Kinder mit AOM: 209 ohne Erregernachweis, 879 mit Erregernachweis
- Demographische Daten und bisheriger Krankheitsverlauf ähnlich

Ergebnis

- Keine Unterschiede zwischen beiden Gruppen im Therapieansprechen

Kommentar

- PCR-Methoden erhöhen die Sensitivität der Diagnostik.
- Allerdings sind diese Methoden für die kinderärztliche Praxis und damit für den Großteil der Patienten zu aufwändig.
- Das deutsche Vorgehen mit Erregernachweis bei ausgewählten Indikationen (z.B. schwerer Verlauf, unzureichende Therapiewirkung) ist plausibel, wobei allerdings Veränderungen der Erregerepidemiologie nicht erkannt werden.

Akute Otitis Media: Therapie mit Makroliden

Hintergrund

- Obwohl Leitlinien die Therapie der AOM mit Makroliden in der Regel nicht empfehlen, werden sie u.a. aufgrund der kurzen Therapiedauer immer wieder verschrieben

Metaanalyse

- 10 randomisierte, verblindete Studien (insgesamt 2766 Patienten; publiziert zwischen 1980 und 2008)
- Vergleich Amoxicillin bzw. Amoxicillin/Clavulansäure versus Makrolid
- Endpunkt: Therapieversagen/Rezidiv 10-16 Tage nach Therapiebeginn

Ergebnis

- Über 30% Therapieversager bei Therapie mit Makroliden
- Signifikant schlechteres Therapieergebnis als Vergleichsarm ($p = 0,008$)

Kommentar

- Die Metaanalyse zeigt eindeutig die Unterlegenheit von Makroliden vs. Amoxicillin bzw. Amoxicillin/Clavulansäure bei AOM.
- Dies sollte bei der Wahl des Antibiotikums unbedingt berücksichtigt werden.

Akute Otitis Media: Zusammenfassung

- Die AOM ist eine der häufigsten Infektionskrankheiten im Kindesalter.
- Diagnostisches und therapeutisches Vorgehen sind dennoch oft unklar und werden kontrovers diskutiert.
- Trotz neuer Ansätze gibt es keine wesentlichen neuen Aspekte in der Diagnostik von Kindern mit AOM.
- Es bestehen weiter Schwierigkeiten bei der initialen Einschätzung des weiteren Verlaufs.
- Neue Methoden wie *Scoring*-System oder Multiplex-PCR sind in der Routinesituation unpraktikabel.
- Das deutsche Vorgehen (invasive Diagnostik zur Erregeridentifikation nur in speziellen Fällen) erscheint angesichts der Datenlage weiterhin plausibel.
- Theorie und Praxis der Therapie unterscheiden sich oft deutlich.
- Makrolide sind mit hohen Therapieversagensraten assoziiert.
- Die Entwicklung neuer Substanzen mit möglichst kurzzeitiger Anwendung wären wünschenswert.



Antimikrobielle Therapie im Kindesalter

Antimikrobielle Therapie im Kindesalter

Hintergrund

- Gerade in Neugeborenenperiode beeinflussen Reifungsprozesse der Exkretionsorgane wie Leber und Niere die Metabolisierung und Ausscheidung vieler Substanzen.
- Einheitliche Dosierungsvorgaben nach Körpergewicht oder Körperoberfläche sind im Kindesalter nicht möglich (z.B. Neugeborene versus Adoleszente).
 - ▶ Unterdosierung → Effektivität ↓
 - ▶ Überdosierung → Toxizität ↑
- Für viele Substanzen besteht Unsicherheit in der Dosierung bei Kindern, da keine oder ungenügende Daten für pädiatrische Patienten vorliegen.

Beispiel

- Retrospektive Analyse der Anwendung von Fluconazol bei Kindern mit Leukämie:
 - ▶ Angewandte Dosierungen lagen zwischen 1 und 29 mg/kg pro Tag (Lehrnbecher et al. EJCMI 2007)

Vancomycin im Kindesalter

Hintergrund

- Bei Erwachsenen mit MRSA-Infektionen sollte eine Vancomycin-Exposition von $AUC_{24}/MHK >400$ erreicht werden

Analyse publizierter Pharmakokinetikdaten

- Vancomycin bei Kindern mit MRSA-Infektionen (Alter 2-12 Jahre)
- 40 mg/kg·d (übliche Empfehlung) vs. 60 mg/kg·d (bei Meningitis empfohlen)

Ergebnis

- 40 mg/kg·d sind bei MRSA mit $MHK \geq 1 \mu\text{g/ml}$ für alle pädiatrischen Altersgruppen in allen verwendeten Analysemodellen unzureichend.
- 60 mg/kg·d erscheinen geeignet.

AUC_{24} = Konzentrations-Zeitintegral im Plasma über 24 h
MHK = minimale Hemmkonzentration

Antimykotische Therapie im Kindesalter

Micafungin

- Neugeborene/junge Säuglinge (2 Tage bis 3 Monate; n = 13)
- 10 mg/kg Einzeldosis: gut verträglich, ausreichende Exposition

Caspofungin

- Kinder (3 Monate bis 17 Jahre)
- Gemeinsame Auswertung mehrerer klinischer Studien
- Empfohlene Dosierung 50 mg/m²·d nach 70 mg/m² *Loading* Dosis
- Alter <3 Monate: 25 mg/m²·d (Saez-Llorens et al.)
- Trotz erhöhter C_{max}- und AUC-Werte keine Häufung unerwünschter Wirkungen

Liposomales Amphotericin B

- Immunsupprimierte Kinder (1-17 Jahre; n = 40)
- Dosisescalation 2,5 bis 10 mg/kg·d
 - ▶ Nebenwirkungen (K⁺ ↓, Dyspnoe) bei 11%, insbesondere bei höheren Dosen
 - ▶ Pädiatrische Dosierung entspricht der Erwachsendosierung

Antimikrobielle Therapie im Kindesalter

Kommentar

- Bei der antimikrobiellen Therapie im Kindesalter sind folgende Aspekte zu beachten:
 - Erregerepidemiologie und Empfindlichkeitsdaten sind wichtig und können die Dosierung unmittelbar beeinflussen.
 - Daten aus Modellanalysen müssen immer mit Daten der klinischen Situation abgeglichen werden (z.B. Modellanalyse zur Effektivität versus Therapieeffektivität in klinischen Studien).
 - Bei liposomalen Amphotericin B entspricht die pädiatrische Dosierung der bei Erwachsenen empfohlenen.
 - Caspofungin sollte entsprechend aktuellen Empfehlungen bei Kindern wie folgt dosiert werden:
 - Alter < 3 Monate: 25 mg/m²·d
 - Alter > 3 Monate: 50 mg/m²·d nach 70 mg/m² Initialdosis; (max. 70 mg/d)
 - Für Micafungin müssen die berichteten Resultate weiter validiert werden, da sie von der bisherigen Dosisempfehlung (Neugeborene bis 16 Jahre: 2 mg/kg·d) stark abweichen.



Abstracts

A-005

Safety, Tolerability and Pharmacokinetics of Liposomal Amphotericin B in Immunocompromised Pediatric Patients

T. J. WALSH¹, A. SHAD ², I. BEKERSKY ³, C. GONZALEZ ², A. H. GROLL ⁴, L. V. WOOD ¹, D. BUELL ³, N. L. SEIBEL ⁵,
¹NCI, Bethesda, MD, ²Georgetown Univ. Med. Ctr., Washington, DC, ³Astellas, Deerfield, IL, ⁴Univ. Children's Hosp., Münster, Germany, ⁵Children's Natl. Med. Ctr., Washington, DC.

Background: Liposomal amphotericin B (L-AMB) is used for treatment of life-threatening mycoses in pediatric patients (pts). However, little is known about its safety, tolerability, and pharmacokinetics in this population.

Methods: L-AMB was studied in 40 immunocompromised children and adolescents in an open-label, sequential, dose-escalation, multidose pharmacokinetic study with 10 to 13 pts in each of four dosage cohorts. Each cohort received daily dosages of 2.5, 5.0, 7.5 or 10 mg/kg L-AMB. Neutropenic pts between the ages of 1 and 17 years were enrolled if eligible to receive empirical antifungal therapy for persistent fever of > 96h despite antibacterial therapy or for treatment of documented invasive fungal infection. Pharmacokinetic parameters were measured as those of amphotericin B by HPLC and calculated by noncompartmental methods.

Results: Mean age was 7.8 ± 5.2 y. Median duration on study was 9.2d. There were 9 adverse event-related discontinuations, 4 of which were related to infusions. Infusion-related side effects occurred in 63 (11 %) of 565 infusions with 5 pts experiencing acute infusion related reactions (7.5 and 10 mg/kg dose levels). Serum creatinine increased from 0.45 ± 0.04 mg/dl to 0.63 ± 0.06 mg/dL ($p=0.003$) at end of therapy. At higher dosage levels of 7.5-10 mg/kg, there was a trend toward greater hypokalemia, azotemia, and infusion related dyspnea, vomiting, chills and rigors. The AUC_{0-24} values of L-AMB on day 1 ranged from 54.7 ± 32.9 at 2.5 mg/kg to 430 ± 566 $\mu\text{g}\cdot\text{h}/\text{ml}$ at 10.0 mg/kg, which were similar to those seen in adult pts. Clearance was not significantly changed across dosages.

Conclusions: These findings indicate that L-AMB can be administered to pediatric patients at dosages similar to those of adults.

A-006

Population Pharmacokinetics and Pharmacodynamics of Caspofungin in Pediatric Patients

C. LI¹, P. SUN¹, Y. DONG¹, S. BI¹, R. DESAI¹, M. FALLON², N. KARTSONIS¹, J. STONE¹;

¹Merck Res. Lab., West Point, PA, ²Vistakon, Jacksonville, FL.

Background: Caspofungin (Cancidas[®]), an echinocandin antifungal administered once daily as 1-hr IV infusion, has been evaluated in 4 pediatric studies of children & adolescents (3 months to 17 y.o.).

Methods: AUC_(0-24hr), End-of-infusion (C_{1hr}) and trough (C_{24hr}) concentrations were obtained in 32, 10, and 82 pediatric patients with invasive candidiasis (IC), invasive aspergillosis (IA), or on empirical therapy who received 50 mg/m² once daily with or without a 70 mg/m² loading dose on Day 1. Odds ratios were estimated for the association between the log-transformed PK and treatment outcomes or adverse experiences (AEs). The potential for covariates (age, gender, weight, race, renal status, serum albumin level, disease state) to predict log-transformed PK was evaluated using a multiple linear regression model. Univariate drug interaction screens compared PK in patients receiving a concomitant medication (>90% of therapy) to patients never receiving that medication.

Results: No PK parameter or hybrid parameter (AUC:MIC, C_{1hr}:MIC and C_{24hr}:MIC) was found to be significantly correlated with treatment outcome or AEs. This result in pediatric patients is consistent with results in adults and suggests that concentrations examined fall near the top of the efficacy concentration-response curve. Weight and disease state had statistically significant (p<0.05), but clinically unimportant small effects on PK. Concomitant use of dexamethasone (CYP inducer) was associated with statistically significant reduction (44%) in C_{24hr}, in a limited number of patients (n=4). Exposures (C_{1hr}, C_{24hr}, and AUC_{0-24hr}) were modestly higher in pediatric patients than in adults receiving 50 mg daily (70 mg load).

Conclusions: The population PK and PK/PD results in pediatric patients were supportive of a 50 mg/m² daily dosing regimen (70 mg/m² load) in children ages 3 months to 17 years. Coadministration of CYP inducers may result in clinically meaningful reductions in PK.

A-012

Safety and Pharmacokinetics (PK) of Repeat-Dose Micafungin (MICA) in Neonates

D. K. BENJAMIN JR¹, P. B. SMITH¹, A. ARRIETA², L. CASTRO³, P. SANCHEZ⁴, D. KAUFMAN⁵, L. ARNOLD⁶, L. KOVANDA⁶, T. SAWAMOTO⁶, D. N. BUELL⁶, W. W. HOPE⁷, T. J. WALSH⁸;

¹Duke Univ., Durham, NC, ²CHOC, Orange, CA, ³Children's Mercy, Kansas City, MO, ⁴UT Southwestern, Dallas, TX, ⁵Univ of Virginia, Charlottesville, VA, ⁶Astellas Pharma US Inc, Deerfield, IL, ⁷Univ of Manchester, Manchester, United Kingdom, ⁸NCI, Bethesda, MD.

Background: Disseminated candidiasis and hematogenous *Candida* meningoenophalitis (HCME) are leading causes of morbidity and mortality in premature infants. Experimental models of HCME and human bridging studies of echinocandin therapy suggest that relatively high weight-based dosages are required for successful therapy. We therefore determined the safety and PK of high dose MICA in infants at risk of invasive fungal infections.

Methods: Open-label PK and safety of repeated dose IV MICA were assessed in young infants > 48 hours of age and < 120 days of life. Infants <1000 grams (g) received 10 mg/kg/day while infants [≥] 1000 g received 7 mg/kg/day once daily for 4-5 consecutive days. Plasma samples were drawn on day 4. MICA concentrations were measured using validated liquid chromatography with tandem mass spectrometric detection.

Results: 13 infants were enrolled; 7 received 7 mg/kg and 6 received 10 mg/kg. Mean baseline weight and gestational age were 2101 g and 688 g, and 30 wks and 25 wks in the 7 mg/kg and 10 mg/kg groups, respectively. 12/13 infants were < 34 wks, 1 was 40 wks, gestational age. Adverse events (AE) occurred in 12/13 infants; drug-related AEs occurred in 3 infants (increased alkaline phosphatase, phlebitis, hypokalemia, temperature elevation). No deaths occurred. Median PK values for the 7 and 10 mg/kg groups, respectively, were: AUC, 258.1 and 291.2 µg*h/mL; Cl_{ss} 0.45 and 0.57 mL/min/kg; C_{max}, 23.3 and 24.9 µg/mL; and V_{dss}, 341.4 and 542.8 mL/kg.

Conclusions: MICA doses up to 10mg/kg were well tolerated and provided exposure adequate for CNS coverage, as suggested by animal data. These data also suggest a single dose level of MICA may be appropriate for neonates, regardless of weight.

C2-242

Changing Patterns in Incidence, Serotype (ST) Distribution, and Antibiotic Resistance of Invasive Pneumococcal Disease (IPD) in Dallas, TX Children, 1999-2007

C. TECHASAENSIRI¹, A. F. MESSINA¹, K. KATZ¹, N. AHMAD², G. H. MCCRACKEN¹;

¹Univ. of Texas Southwestern Med. Ctr. at Dallas, Dallas, TX, ²Children's Med. Ctr. of Dallas, Dallas, TX.

Background: Administration of the heptavalent pneumococcal conjugate vaccine (PCV7) has reduced vaccine-type (VT) invasive pneumococcal disease (IPD) in children. An increasing percentage of IPD cases is now caused by non-vaccine (NVT) serotypes. We analyzed the serotype and antimicrobial resistance patterns among *S. pneumoniae* (SP) responsible for IPD at Children's Medical Center, Dallas (CMCD) from 1999 through 2007.

Methods: SP isolated from normally sterile sites were collected from January 1, 1999 through December 31, 2007. Incidence of IPD was calculated using inpatient and emergency center admissions to CMCD as the denominator. SP isolated were serotyped by quellung reaction and penicillin and cefotaxime susceptibility were determined by E-test. Serotype 19A isolates were characterized by PFGE and by multi-locus sequence typing (MLST).

Results: The incidence of IPD per 100,000 patients decreased 56% from 93.6 in 1999 to a nadir of 41 in 2003 ($P < 0.001$); subsequently the rates (per 100,000 patients) were 64.2 in 2005 ($p = 0.039$ vs 2003), 45 in 2006, and 60 in 2007. The number of IPD cases caused by serotype 19A increased 85% from 1999 through 2005 ($p < 0.001$) at which time it comprised 20 of the 49 (41%) IPD isolates. The number of 19A isolates causing IPD decreased to 8 of 36 (22%) in 2006 but increased to 16 of 50 (32%) in 2007. As determined by MLST, the most common sequence type (ST) of the 19A isolates was ST-199, representing 35 of 71 (49.3%) isolates. In 2007 there was an increased percentage of IPD cases caused by cephalosporin resistant strains. All serotype 19A isolates in 2007 were penicillin non-susceptible.

Conclusions: In Dallas, PCV7 immunization has eliminated IPD caused by VT serotypes but the overall incidence of IPD in 2007 was reduced only 36% compared with that in 1999. Many of the NVT strains are resistant to beta-lactam antibiotics.

C2-247

Impact of 7-Valent Pneumococcal Conjugate (PCV7) on Serotype Distribution and Susceptibility Profiles of Invasive *S. pneumoniae* (ISp) Isolates in Quebec

L. JETTÉ¹, A. BOURGAULT¹, L. RAYNAL¹, P. DE WALS²;

¹Laboratoire de santé publique du Québec/Inst. Natl. de santé publique du Québec, Montreal, Canada, ²Dept. of Social and Preventive Med. Université Laval, Quebec City, Canada.

Background: In December 2004, PCV7 was introduced in the publicly-funded immunization program in the province of Quebec using a 3-dose (2, 4, 12 months) schedule for low risk infants. The laboratory surveillance program was enhanced to document the evolution in the serotype distribution and susceptibility profiles of ISp isolates.

Methods: ISp isolates from children < 5 yo were received from sentinel laboratories and were serotyped (capsular staining) and tested for antimicrobial susceptibility by a microdilution method. Starting in January 2005, all laboratories were invited to transmit all isolates from children < 5 yo.

Results: From 2005 to 2007, 299 ISp were analyzed. The number and proportion of PCV7 serotypes decreased steadily : 67/114 (59%) in 2005, 20/76 (26%) in 2006 and 12/109 (11%) in 2007. 19A was the main emerging serotype (10% in 2005 to 25% in 2006 and 2007). It was more frequently isolated from children < 2 yo (42/59, 71%) and was found to be multiresistant (25/59, 42%). Historic data showed that the proportion of ISp caused by PCV7 serotypes varied between 79% to 86% in the 2000-2004 period but was only 7% in 2007. Mean resistance rates were: penicillin G (11.9%: from 17.6% in 2004 to 8.1% in 2007); chloramphenicol (7.6%); clindamycin (23.2%); erythromycin (33.1%: from 43.4% in 2004 to 21.6% in 2007); TMP-SMX (19.2%). Among strains isolated from CSF, only one was resistant to ceftriaxone. No strain was found to be resistant to vancomycin or levofloxacin.

Conclusions: The introduction of PCV7 was followed by an important decrease of vaccine related serotypes and the emergence of 19A serotype strains, especially among children < 2 yo. Overall, resistance rates to penicillin G and macrolides decreased over time. More surveillance is needed to further characterize the evolution of serotype and resistance patterns.

G-2110

Surveillance of IPD in Children in Germany 2004 - 2008, First Results of the German National Immunization Program for PCV7

M. VAN DER LINDEN¹, M. IMOEHL¹, R. REINERT²;

¹Inst. of Med. Microbiol., Aachen, Germany, ²Wyeth Vaccines Res., Paris, France.

Background: Since 1997 the German National Reference Center for Streptococci has monitored the epidemiology of invasive pneumococcal disease (IPD) in German children up to 15 years of age. In July 2006 evidence of the beneficial effects of a heptavalent conjugate vaccine on the incidence of IPD led to a general recommendation for the vaccination with a 7-valent pneumococcal conjugate vaccine (PCV7) for all children up to the age of 24 months. As from January 2007 approximately 80 % of all newborns in Germany have been vaccinated with at least one dose of PCV7. In this study we have monitored the effects of PCV7 on the incidence of IPD in Germany.

Methods: Cases of IPD in children were reported by microbiological laboratories and pediatric hospitals. Species confirmation was done by optochin testing, bile solubility and serotyping. Serotyping was performed using the Neufeld Quellung reaction.

Results: For children 0-23 months of age, in the period July 2007-March 2008 (n=85), 34 cases caused by PCV7 serotypes were reported. In the same period the year before (n=106) 69 PCV7 cases were reported. This represents a 50% reduction. The most significant reduction was seen in serotype 14: 12 cases in July 2007- March 2008 as compared to 25 cases in July 2006 - March 2007. Serotype 14 has been by far the most prominent serotype among IPD in children in the 10 years before introduction of the vaccine (25% of all cases). The amount of non-PCV7 cases did not differ from the year before. An effect in age groups 24-59 months and 60-192 months was not seen.

Conclusions: First effects of PCV7 are seen in IPD cases in German children less than 2 years of age. This effect is most significant for serotype 14 cases. An effect in age groups 2-15 years of age was not yet observed.

G-2111

Changes in the Epidemiology of Invasive Pneumococcal Disease (ipd) Following Implementation of a 7-Valent Pneumococcal Conjugate Vaccine (pcv7) Program in Quebec, Canada

P. DE WALIS¹, L. JETTÉ ², É. SEVIN ³, M. OUAKKI ³, M. DOUVILLE - FRADET ³, F. MARKOWSKI ⁴, D. BOLDUC ⁴, G. DECEUNINCK ⁵;

¹Laval Univ., Quebec City, Quebec, Canada, ²Quebec Natl. Publ. Hlth.Inst., Quebec City and Montreal, Canada, ³Quebec Natl. Hlth.Inst., Quebec City and Montreal, Canada, ⁴Quebec Ministry of Hlth.and Social Services, Montreal, Canada,

⁵Quebec Univ. Hosp. Res. Ctr., Quebec City, Canada.

Background: In December 2004, a 3-dose (2, 4, & 12 months) PCV7 program was implemented for routine immunization of infants along with “passive” catch-up vaccination for children aged up to 4 years. Uptake was high and 90% of children aged 2 months at the launch of the program had received ³ 3 doses by age 2 years.

Methods: IPD cases were extracted from the provincial registry of notifiable disease, which is essentially based on reports from public hospital laboratories and the provincial reference laboratory. Age-specific trends in IPD incidence and serotype distribution were calculated.

Results: Overall IPD incidence decreased from 10.9/100,000 person-years in 1999-2001 (before PCV was licensed in Canada) to a minimum of 8.6/100,000 in 2006, and increased to 9.8/100,000 in 2007. The same pattern was observed in all age groups. The initial decrease was associated with a diminishing occurrence of PCV7 serotypes and was most marked in children aged less than 2 years. In this age group, the incidence of PCV7 serotypes (adjusted for incomplete serotype identification) decreased from 87.3/100,000 in 1999-2001, to 4.4/100,000 in 2007 (95% reduction). The secondary increase was caused by PCV-related serotypes (mainly 19A), and non-PCV7 serotypes (mainly 12F, 33A and 7F), and was also more marked in children less than 2 years than in older age groups.

Conclusions: Direct vaccine protection in conjunction with herd immunity are competing with clonal evolution and ecological replacement involving *Sp* serotypes not included in or imperfectly covered by PCV7. Nobody knows where and when equilibrium between these two antagonist forces will be reached.

G-2116

A Phase 3 Trial Evaluating the Safety, Tolerability and Immunogenicity of Manufacturing Scale 13-valent Pneumococcal Conjugate Vaccine

J. GADZINOWSKI¹, S. TANSEY², T. MELLELIEU², S. BAKER³, P. C. GIARDINA³, W. C. GRUBER³, **D. A. SCOTT**³;
¹Dept. of Neonatology, Univ. of Med. Sci., Poznan, Poland, ²Wyeth Vaccines Res., Taplow, Maidenhead, United Kingdom, ³Wyeth Vaccines Res., Pearl River, NY.

Background: 13-valent pneumococcal conjugate vaccine (PCV13) includes 6 polysaccharide antigen serotypes in addition to those included in the currently licensed 7-valent vaccine. It was developed to give improved worldwide protection against vaccine-preventable invasive pneumococcal disease (IPD). Objectives of the current study were to demonstrate that manufacturing scale PCV13 (PCV13 manu) is clinically similar to pilot scale PCV13 (PCV13 pilot) used in earlier clinical studies. **Methods:** Subjects 2 months of age (N=269) were randomly assigned (1:1 ratio) to receive PCV13 pilot or PCV13 manu at 2, 3, and 4 months of age. Serum concentrations of anticapsular immunoglobulin G (IgG) for each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) were determined 1 month after the infant series (at 5 months). Local reactions and systemic events were recorded in e-diaries for 4 days after each vaccination. **Results:** For the PCV13 pilot and PCV13 manu groups respectively, the proportion of subjects achieving pneumococcal IgG antibody ³0.35 µg/mL was >90% for 9 and 10 of the 13 serotypes and was ³74% for both groups for all 13 serotypes. The proportion of subjects achieving pneumococcal IgG antibody ³0.35 µg/mL was similar for both groups; the difference in proportion of responders (PCV13 manu - PCV13 pilot) for the 13 serotypes ranged from -1.7% to 3.3%. The percentages of subjects reporting local reactions and systemic events were comparable between the two groups. **Conclusions:** The safety and immunogenicity of PCV13 manu are similar to that of PCV13 pilot after administration at 2, 3, and 4 months of age.

G-2117

Safety & Immunologic Non-Inferiority of 13-Valent Pneumococcal Conjugate Vaccine Compared to 7-Valent Pneumococcal Conjugate Vaccine Given with Routine Vaccines in Healthy Infants

D. M. KIENINGER¹, K. KUEPER ¹, K. STEUL ¹, C. JUERGENS ², N. AHLERS ², S. BAKER ³, P. GIARDINA ³, W. GRUBER ³, D. SCOTT ³;

¹Zentrum für Kinder- und Jugendmedizin an der Johannes Gutenberg-Univ. Mainz, Mainz, Germany, ²Wyeth Res, Münster, Germany, ³Wyeth Vaccines Res, Pearl River, NY.

Background: 7-valent pneumococcal conjugate vaccine (PCV7, Prevenar®) is effective against vaccine-serotype invasive pneumococcal disease in children; addition of serotypes 1, 3, 5, 6A, 7F, and 19A broadens coverage worldwide.

Objectives: safety and immunogenicity of PCV7 compared to 13-valent pneumococcal conjugate vaccine (PCV13; serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F).

Methods: Infants were randomly assigned to receive PCV13 or PCV7 (1:1 ratio) at 2, 3, 4 mo of age with Infanrix® hexa (GSK; DTaP-IPV-HepB-Hib). Antibody responses to the pneumococcal vaccine, Hib, diphtheria, and Hep B antigens were measured 1 month after dose 3. Local and systemic reactions were assessed.

Results: From 604 infants, 293 in each group completed the series. For PCV13 and PCV7 groups 77.5 to 98.9% and 87.1 to 98.6% subjects achieved serum IgG levels [≥]0.35 mg/mL for each of the 7 common serotypes. For the 6 additional serotypes 91.9 to 99.3% of subjects in the PCV13 group responded. Using the % responders at 0.35 mg/mL, noninferiority criteria were met for 12 of 13 serotypes; 6B responses in PCV13 compared to PCV7 recipients were -9.6% (95% CI -16.0, 3.3). Using responders at [≥]0.15 mg/mL and geometric mean concentrations (GMCs), noninferiority criteria were met for all 13 serotypes.

In the PCV13 and PCV7 groups for Hib 89.5% and 86.9% achieved 0.15 mg/mL; diphtheria 89.7% and 94.2% achieved 0.1 IU/mL; and Hep B 94.9% and 96.3% achieved [≥]10.0 mIU/mL. Systemic and local reactions were similar in both groups.

Conclusions: 1. PCV13 met predefined non-inferiority criteria to PCV7 for all serotypes using responders at [≥]0.15 mg/mL and GMCs, and for all at [≥]0.35 mg/mL except for 6B. 2. For Hib, diphtheria, and Hep B, responses were similar. 3. Reactogenicity profiles were similar.

G2-1270

Current Recommendations for Vancomycin Dosing are Inadequate for Children with Invasive MRSA Infections

A. FRYMOYER, A. L. HERSH, L. Z. BENET, B. J. GUGLIELMO;
Univ. of California San Francisco, San Francisco, CA.

Background: Vancomycin (VAN) $AUC_{24}/MIC > 400$ is associated with optimal outcomes in treatment of invasive *methicillin-resistant Staphylococcus aureus* (MRSA) infections in adults. It is unknown whether recommended VAN dosing regimens for children achieve this level. Our objective was to determine whether currently recommended VAN dosing regimens in children result in VAN $AUC_{24}/MIC > 400$.

Methods: A VAN dose of 40 mg/kg/day was used for calculations, since this dose is recommended by all primary pediatric dosing references. AUC_{24} was calculated as Daily Dose/VAN Clearance (CL). Two approaches were used to estimate VAN CL in children: 1) previously reported VAN CL in literature and 2) calculated VAN CL using previously proposed models and a hypothetical population of healthy children. AUC_{24}/MIC were calculated from the above mentioned dose, VAN CL, and MIC.

Results: The MIC_{50} for pediatric MRSA isolates in the previous year at UCSF Children's Hospital was 1.0 mg/ml. At the recommended dose of 40mg/kg/day and reported VAN CLs, predicted AUC_{24}/MIC ranged from 271 to 388 when $MIC = 1.0$ mg/ml. Similarly, models of vancomycin clearance in healthy children routinely predicted $AUC_{24}/MIC < 400$. These findings were consistently demonstrated for children of all ages.

Conclusions: 1) Despite the use of multiple prediction models, recommended pediatric VAN dosing does not achieve $AUC_{24}/MIC > 400$ in children for MICs ≥ 1.0 mg/ml. 2) If $AUC_{24}/MIC > 400$ is associated with optimal outcomes for children as it is for adults, increased VAN doses are required in children.

G2-1303

New Acute Otitis Media Symptom Score System Produces Superior Differentiation of Cure versus Failure Outcomes

J. R. CASEY¹, S. BLOCK², P. PUTHOOR¹, J. HEDRICK², A. ALMUDEVAR¹, M. PICHICHERO¹;

¹Univ. of Rochester, Rochester, NY, ²Kentucky Pediatric Res., Bardsville, KY.

Background: Diagnosis and outcome evaluation of Acute Otitis Media (AOM) in clinical trials could be aided by a precise and reproducible scoring system. We compared a 10 point and a 30 point scoring system based on common symptoms and signs associated with AOM.

Methods: Symptoms (fever, level of ear pain and irritability) associated with AOM described by parents and signs (temperature, tympanic membrane (TM) erythema, mobility, color, position and presence of otorrhea) of AOM observed by validated otoscopists at 2 AOM research centers were tabulated and scored at acute onset of illness and at the test of cure visit.

Results: 330 subjects with an average age 13.1 months (SD = 4.9) were diagnosed with AOM. The 10 point and the 30 point scoring systems were highly correlated $r=0.72$; $p < 0.001$ at the time of diagnosis; no additional discriminatory power was gained with the 30 point scale. At the test of cure visit 256 children were cured and 71 failed. The mean follow-up scores for the 10 point scoring system were 0.48 (SD=0.84) and 4.42 (SD=1.76) for children with cure and failure; and 2.17 (SD=2.58) and 12.04 (SD=4.80) for the 30 point scoring system respectively. The 10 point scoring system was more discriminatory in correlating with the final AOM diagnosis. Inter-observer agreement using the two scoring systems was high.

Conclusion: Both a 10 and 30 point AOM scoring systems were highly correlated when AOM was present and both discriminated AOM cure and failure. The 10 point scoring system might be preferred because it was superior in differentiating cure and failure and simpler to use.

G2-1304

A Comparison of Pathogens Causing Acute Otitis Media in Children with the First or Second Episode versus Recurrent and Difficult-to-Treat Episodes

J. R. CASEY, D. ADLOWITZ, M. E. PICHICHERO;
Univ. of Rochester, Rochester, NY.

Background: Much is understood about the microbiology of Acute Otitis Media (AOM) in recurrent or difficult-to-treat infections but this is the first report in the US of the microbiology of AOM in children with their first or second episode of AOM.

Methods: Two groups were studied prospectively to determine the microbiology of AOM episodes: (1) children without a history of AOM and (2) children with recurrent or difficult-to-treat AOM. Most children were less than 2 years old who had received the 7 valent pneumococcal conjugate vaccine.

Results: We have studied 100 AOM episodes in 152 children thus far. Among 88 children enrolled at 6 months of age, 24 had 1 AOM infection, 7 had 2 AOM infections, and 1 had 4 infections, total = 35 AOM episodes. 64 children with 65 recurrent or difficult-to-treat AOM infections were also studied in comparison. The proportion of *S. pneumoniae* isolates from the middle ear fluid (MEF) was 23% and 25%, for *H. influenzae* was 31% and 38%, for *M. catarrhalis* was 9% and 5%, and 2 pathogens were found in 3% and 5% for the AOM infrequent group and the recurrent or difficult-to-treat group respectively. The serotypes of the *S. pneumoniae* isolates were 19A (38%), 23A (12.5%), other (12.5%) and to be typed (50%) in the infrequent AOM group and 19A (45%), 6A (15%), other (10%) and to be typed (20%). Antibiotic susceptibility testing is planned.

Conclusion: This is the first study of US children to compare the microbiology from initial and second AOM episodes with recurrent or difficult-to-treat AOM episodes. The microbiology does not differ between the two groups and 19A is the most commonly isolated *S. pneumoniae* serotype in either group. Supported by NIH, NIDCD RO1DC008671 and the Thrasher Research Fund

G2-1305

Clinical Outcome in Children with Culture-Negative (Cx-) Acute Otitis Media (AOM)

E. LEIBOVITZ, E. NAKASH, N. GIVON-LAVI, R. DAGAN;
Ben Gurion Univ and Soroka Univ Med Ctr, Beer-Sheva, Israel.

Background: Cx- AOM is often milder and associated with lower local/systemic inflammatory responses than Cx+ AOM. The objective of the study was to compare clinical outcome of Cx- with that of C+ AOM children.

Methods: AOM children aged 3-35 mo were enrolled in 12 double-tympanocentesis antibiotic efficacy studies documenting both bacteriologic (day 4-6 of Rx) and clinical outcome (end of Rx). Univariate analysis (age, gender, ethnicity, previous AOM history and antibiotic Rx) between Cx- and Cx+ AOM patients was performed by Student's t test, ANOVA or Chi square test. Those found to be significant were further submitted to multivariable regression analysis.

Results: 1088 patients (mean age 11.95 ± 5.96 mo, 209 Cx- and 879 C+ AOM) were enrolled. No differences were recorded between Cx- AOM and Cx+ AOM patients in age, gender, ethnicity and no. of previous episodes. 50% (105/209) Cx- AOM received antibiotics before enrollment vs. 29% (253/879) Cx+ AOM ($P < .001$). 74% (650/879) Cx+ AOM patients achieved bacteriologic eradication within 3-5 days. Successful outcome (cured+improved) was recorded in 90% (189/209) Cx- AOM patients vs. 86% (758/879) in Cx+ AOM ($P = .086$). Successful clinical outcome was more frequent in Cx- than in Cx+ AOM without bacteriologic eradication (90% vs. 67% [154/229], $P < .001$). No difference in successful clinical outcome was found between Cx- vs. Cx+ AOM patients with bacterial eradication (90% vs. 93% [604/650], $P = .24$).

Conclusions: 1) Cx- AOM was similar to Cx+ AOM in demographic, epidemiologic and disease history characteristics; 2) Previous antibiotic Rx decreased significantly the positivity rate of middle ear fluid cultures; 3) Clinical outcome of Cx- AOM was similar to that of Cx+ AOM with bacteriologic eradication and both were superior to that of Cx+ AOM without eradication; 4) Inclusion of Cx- AOM patients in series aiming at antibiotic efficacy may falsely improve clinical outcome when treated with antibiotics with reduced ability to eradicate AOM pathogens.

G2-1306

Multi-Locus PCR (ML-PCR) Detects *Streptococcus pneumoniae* (*Spn*) and *Haemophilus influenzae* (*Hflu*) in Middle Ear Fluids (MEF) that are Culture-Negative from Children with Acute Otitis Media (AOM)

Q. XU M¹, D. G. ADLOWITZ¹, J. R. CASEY^{1,2}, M. E. PICHICHERO^{1,3}, M. ZENG¹;

¹Univ. of Rochester, Rochester, NY, ²Legacy Pediatrics, Rochester, NY, ³Legacy Pediatrics, Rochester, NY.

Background: We are studying the systemic and mucosal immune responses to candidate antigens of *Spn* and *Hflu* that might be used to reduce or prevent AOM by these bacteria. Some *Spn* and *Hflu* strains may not grow well and be identified by current bacterial culture techniques. Accurate detection of *Spn* and *Hflu* in MEF therefore becomes critical.

Methods: Bacterial genomic DNA was extracted from culture negative MEF of children with AOM. Some children were culture positive in the nasopharynx (NP) or throat and others were culture negative in the NP and throat. The internal fragments of 7 house keeping genes were amplified by ML-PCR, followed by multi-locus sequencing typing (MLST) for *Spn* and *Hflu* if all seven genes were amplifiable.

Results: 14 *Spn* and 22 *Hflu* culture-positive MEF were all positive in ML-PCR; all 7 house keeping genes were amplifiable by ML-PCR, and MLST analysis confirmed that they were *Spn* or *Hflu* isolates. 16 of 18 (89%) children with AOM who had *Spn* culture negative in MEF but positive in NP or throat, were *Spn* DNA positive detected by ML-PCR in MEF; 9 of 12 (75%) MEF that were culture negative for *Hflu* had *Hflu* DNA shown by ML-PCR when the NP or throat cultures were positive for *Hflu*; among those 2 groups of ML-PCR positive MEF, only 3 of 16 (18 %) *Spn* positive samples and 1 of 9 (11%) *Hflu* positive samples were typeable by MLST since all 7 genes could not be amplified simultaneously. In MEF from children with AOM who were culture negative in all sources, 49 % (19/39) and 33% (6/18) were ML-PCR positive for *Spn* and *Hflu*, respectively, but none of these isolates was typeable by MLST.

Conclusions: ML-PCR significantly improves accurate identification of the presence of the otopathogens *Spn* and *Hflu* in MEF of children with AOM when cultures are negative. *Spn* and *Hflu* likely account for a large proportion of AOM cases that are culture negative in MEF.

G2-1308

Are Macrolides as Efficacious as Guidelines Recommended Antibiotics in the First-Line Treatment of Children with Acute Otitis Media? A Meta-Analysis

J. D. COURTER¹, W. L. BAKER², K. S. NOWAK³, L. A. SMOGOWICZ³, C. I. COLEMAN², J. E. GIROTTO¹;
¹CCMC & UCONN, Hartford, CT, ²Hartford Hosp & UCONN, Hartford, CT, ³UCONN, Storrs, CT.

Background: Macrolide antibiotics are often used to treat children with acute otitis media (AOM); however, the American Academy of Pediatrics & American Academy of Family Physicians guidelines recommend against their use unless patients have previously presented with a type I allergic reaction to penicillins. Therefore, we performed a meta-analysis of randomized controlled trials to evaluate the comparative efficacy of amoxicillin or amoxicillin/clavulanate to that of macrolide antibiotics in the treatment of children with AOM.

Methods: A systematic literature search was conducted in the MEDLINE, EMBASE and the International Pharmaceutical Abstract databases from 1/1980-4/2008. Studies were eligible if they were randomized, blinded and controlled trials evaluating guideline recommended antibiotics (amoxicillin or amoxicillin/clavulanate) to macrolides in AOM in children. The primary outcome measures assessed was the percentage patients experiencing clinical failure measured between days 10-16 after starting antibiotic therapy. Results are reported as relative risks (RRs) with 95% confidence intervals and were calculated using a random-effects model.

Results: A total of 10 trials (n=2,766) were included in the meta-analysis. Upon meta-analysis, the use of macrolide antibiotics was associated with an increased risk of clinical failure [RR; 1.31 (95%CI 1.07 to 1.60; p=0.008)] corresponding to a number needed to harm of 32. No statistical heterogeneity was observed between studies ($I^2=0\%$) and review of the funnel plot and Egger's weighted regression statistics (p=0.82) suggested a low likelihood of publication bias.

Conclusions: The use of macrolide antibiotics as first line treatment of AOM in children was found to be associated with a 31% increased risk for clinical treatment failure. Our findings support the current AOM recommendation.