**Concorso pubblico, per titoli ed esami, per la copertura a tempo indeterminato di n. 3 posti di Dirigente Medico disciplina Malattie dell'Apparato Respiratorio.**

## Verbale n. 7

Il giorno 2 del mese di luglio 2024 alle ore 12:00 presso l'Aula 1, dell'edificio 4, del P.O. "G. Rodolico" di Catania, si è riunita la Commissione esaminatrice del concorso in epigrafe, per l'espletamento della prova orale.

La Commissione esaminatrice è composta come al precedente verbale n. 1 del 16 maggio 2024.

Il Presidente, constatata la presenza di tutti i Componenti e del Segretario, accertata la legale costituzione della Commissione, dichiara aperta la seduta.

La Commissione, ad inizio dei lavori, prende atto che con pec prot. n. 33915 del 11/06/2024, rettificata relativamente alla sede d'esami giusta pec prot. n. 35229 del 18/06/2024, si è già correttamente provveduto alla convocazione per la data odierna dei candidati idonei per l'espletamento della prova orale prevista dal bando.

La Commissione prende atto, altresì, che è stato reso noto il risultato della valutazione dei titoli, prima dell'effettuazione della prova orale, mediante pubblicazione nella sezione dedicata al concorso all'interno del sito web istituzionale aziendale di apposita tabella contenente la votazione riportata da ciascun candidato convocato per l'ultima prova.

La Commissione, pertanto, così come stabilito nel verbale n. 1:

a. predispone collegialmente n. 50 argomenti/quesiti (quattro in più rispetto ai candidati ammessi alla prova) di uguale complessità ed impegno (**allegato n. 1**), inerenti alla disciplina a concorso, definiti e numerati secondo l'ordine di seguito riportato:

1. Emottisi: eziologia ed approccio diagnostico
2. Ventilazione meccanica non invasiva: indicazioni e controindicazioni
3. OSAS: diagnosi
4. OSAS: trattamento
5. Diagnosi di asma bronchiale
6. Bronchiectasie
7. BPCO: diagnosi
8. Edema polmonare
9. BPCO: terapia
10. BPCO riacutizzata
11. Fibrosi polmonare idiopatica
12. Polmoniti nosocomiali
13. Tumore del polmone: diagnosi e stadiazione
14. Tumore del polmone: approccio terapeutico
15. Pneumotorace
16. I test di funzionalità respiratoria nella pratica clinica
17. Versamento pleurico: diagnosi e trattamento
18. Dispnea: diagnosi differenziale
19. Insufficienza respiratoria acuta

20. Insufficienza respiratoria cronica
21. Polmoniti di comunità: criteri di ospedalizzazione
22. Asma grave
23. Bronchite cronica
24. La terapia dell'asma
25. Insufficienza respiratoria ipercapnica
26. Polmonite da SARS COV-2
27. Enfisema polmonare da deficit di ALFA-1 antripsina
28. La diagnosi di embolia polmonare
29. Asma grave: diagnosi
30. Ossigenoterapia domiciliare a lungo termine: tipologia e prescrivibilità
31. Versamento pleurico: diagnosi differenziale
32. Insufficienza Respiratoria Acuta: indicazione al trattamento con ventilazione non invasiva
33. Nodulo polmonare solitario: iter diagnostico
34. Interstiziopatie polmonari: diagnostica strumentale
35. Polmonite di comunità
36. Polmonite associata alla ventilazione
37. Gestione dell'IR in corso di polmonite da COVID
38. Empiema pleurico
39. Fibrosi polmonare idiopatica
40. Polmoniti da farmaci
41. Polmonite da ipersensibilità
42. Aspergillosi broncopolmonare allergica
43. Bronchiectasie: diagnostica
44. Micobatteriosi atipiche
45. Sarcoidosi
46. Istiocitosi X
47. Indicazioni all'ossigenoterapia
48. Interessamento polmonare nelle connettiviti
49. Polmonite organizzativa
50. Interstiziopatie polmonari fibrosanti

b. sceglie di comune accordo le riviste scientifiche in lingua inglese (**allegato n. 1**), dalle quali saranno estrapolati gli articoli oggetto della lettura e traduzione da parte degli ammessi alla prova, al fine di accertare la conoscenza della lingua inglese, segnatamente:
"*European Respiratory journal*" (Volume 32 e Volume 37).
La Commissione stabilisce, altresì, le parti delle riviste da sottoporre all'esame dei candidati ammessi alla prova che risultano evidenziate e numerate da n. 1 a n. 50 (due in più rispetto ai candidati ammessi alla prova).

c. all'unanimità definisce n. 50 quesiti (due in più rispetto ai candidati ammessi alla prova) di uguale complessità ed impegno, volti ad accertare l'uso delle apparecchiature e delle applicazioni informatiche più diffuse (**allegato n. 1**), che vengono numerati e riportati di seguito:
    1. Che cos'è l'applicativo Word e che utilizzo un utente può farne?
    2. Che cos'è l'applicativo Power Point e che utilizzo un utente può farne?
    3. Che cos'è l'applicativo Excel e che utilizzo un utente può farne?
    4. Un "portale internet" o un "portale Intranet" sono la medesima cosa?
    5. Cos'è Windows Media Player?

6. Cos’è la posta elettronica certificata (PEC)?
7. Che cos’è un “browser”?
8. Che cosa si intende per “antivirus”?
9. Cosa si intende per e-learning?
10. Che cosa si intende con il termine di “periferica”?
11. Se un collega tramite posta elettronica inoltra dei dati su un “foglio di lavoro elettronico” di che software ho bisogno per poterlo aprire ed eventualmente modificare o integrare?
12. Cos’è un motore di ricerca?
13. A cosa serve un backup?
14. La firma digitale.
15. La funzione copia.
16. La funzione incolla.
17. La funzione taglia
18. La funzione cronologia.
19. La funzione dello scanner.
20. La casella di posta elettronica.
21. Le funzioni dell’hard disk.
22. Cos’è la telemedicina?
23. Cos’è una stampante multifunzione?
24. Differenza tra PEC e posta elettronica ordinaria.
25. Differenza tra File e Cartella.
26. Cos'è il desktop?
27. Cosa è Google Chrome?
28. In word è possibile attivare il controllo ortografico?
29. Che cosa è “Outlook Express”?
30. Cos’è per un PC la CPU?
31. Cosa è lo Spamming?
32. Cosa è la tecnologia Bluetooth?
33. La funzione filtro in Microsoft Excel.
34. Cos’è una connessione wireless?
35. La funzione del modem.
36. Cosa significa “zippare” un file.
37. Principali funzionalità di un database.
38. Cos’è il pendrive?
39. L’anteprima di stampa, funzioni e utilità.
40. Quali sono le principali funzionalità di una rete intranet?
41. Quali sono le principali funzionalità del software identificato come “foglio di calcolo”?
42. Cosa è l’hardware in una postazione informatica?
43. Differenza tra hardware e software.
44. Cos’è la RAM?
45. Che cosa si intende per “Firewall”?
46. Che cosa si intende con il termine “Attachment” ed in che ambito lo si può incontrare, e per quali finalità?
47. Se nell’ambito di una riunione si volessero presentare dei risultati con una presentazione al PC quale software risulterebbe più adeguato utilizzare e perché?
48. Cos’è il sistema operativo di un PC?
49. Cosa si intende per dispositivo tablet?
50. Cos’è il pdf?

A questo punto, la Commissione predispone n. 50 bigliettini numerati da 1 a 50 piegandoli in modo tale che il numero non sia visibile, cosicché il candidato da esaminare possa estrarre un numero a sorte equivalente ad un argomento/quesito oggetto d'esame inerente alla disciplina a concorso, ad un brano tratto dalle riviste scientifiche in lingua inglese, ad un quesito riguardante la verifica della conoscenza delle applicazioni informatiche, tra quelli inseriti nell'elenco predisposto dalla Commissione di cui all'**allegato n. 1.**

Quindi collegialmente stabilisce che ciascun candidato presente (**allegato n. 2**):

- *inizialmente* (e secondo l'ordine definito dopo l'estrazione a sorte della lettera che definisce l'ordine di effettuazione della prova) estrarrà a sorte un numero (tra quelli appositamente predisposti dalla Commissione) al quale corrisponde un argomento/quesito oggetto d'esame inerente alla disciplina a concorso, una parte di brano tratto dalle riviste scientifiche in lingua inglese, un quesito riguardante la verifica della conoscenza delle applicazioni informatiche.
  I numeri corrispondenti agli argomenti sorteggiati saranno poi esclusi dalle possibilità di estrazione a sorte per i candidati seguenti;
- successivamente, apporrà la propria firma in un apposito allegato che costituisce parte integrante del presente verbale (**allegato n. 3**) ove è evidenziato l'esito del sorteggio;
- *in seguito*, il candidato relazionerà in merito al contenuto della prova orale dallo stesso estratta a sorte.

Alle 12:15 la Commissione ammette nei locali di esame i candidati, procedendo progressivamente all'appello degli stessi, alla loro identificazione tramite l'esibizione di un valido documento di riconoscimento ed all'apposizione delle relative firme su apposito foglio presenze.

Risultano essere presenti n. 46 candidati, come da elenco presenze allegato e parte integrante del presente verbale (**allegato n. 2**).

Il candidato Alaimo Luana, designato dagli stessi candidati presenti, estrae la lettera "I" che definisce l'ordine dei candidati per l'effettuazione della prova orale.
I colloqui proseguiranno in ordine alfabetico.

La prova orale svolta alla presenza dell'intera Commissione ed in seduta pubblica ha inizio alle ore 12:50, il Presidente della Commissione stabilisce, altresì, di non ammettere a partire da adesso alcun candidato che si dovesse presentare in ritardo per l'effettuazione della prova.

Il Presidente informa i candidati sulle specifiche modalità di effettuazione della prova orale e comunica, inoltre, che l'esito della prova orale sarà pubblicato (come per le prove d'esame precedenti) sull'apposita sezione relativa al concorso del sito internet istituzionale aziendale, al termine della prova in questione.
Si invitano formalmente i candidati presenti, a visionare sul sito internet istituzionale aziendale la valutazione dei titoli, appositamente già pubblicata prima dell'effettuazione della prova d'esame orale.

Il primo candidato interpellato, pertanto, è Giuseppe Ielo che nell'ordine:

- estrae il numero riferito alla prova orale numero "12";
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3);
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell’uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Pietro Impellizzeri che nell’ordine:
- estrae il numero riferito alla prova orale n. 36;
- sottoscrive l’allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell’uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Michele La Rosa che nell’ordine:
- estrae il numero riferito alla prova orale n. 25;
- sottoscrive l’allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 15 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell’uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 1 |
| Punteggio complessivo prova orale: | **17** |

Segue il candidato Santa Valentina Liuzzo che nell’ordine:
- estrae il numero riferito alla prova orale n. 5;
- sottoscrive l’allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 15 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell’uso delle | 1 |

| | |
|---|---|
| apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | |
| Punteggio complessivo prova orale: | **17** |

Segue il candidato Giuliana Luca che nell'ordine:
- estrae il numero riferito alla prova orale n. 41;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

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|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Luca Malandrino che nell'ordine:
- estrae il numero riferito alla prova orale n. 38;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Manuel Mancuso che nell'ordine:
- estrae il numero riferito alla prova orale n. 20;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

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|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 15 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Erica Falzone che ha chiesto alla Commissione la possibilità di anticipare la prova orale in considerazione di particolari esigenze personali

- estrae il numero riferito alla prova orale n. 28;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 1 |
| Punteggio complessivo prova orale: | **18** |

Segue il candidato Giorgio Morana che nell'ordine:

- estrae il numero riferito alla prova orale n. 47;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Giuseppe Muscato che nell'ordine:

- estrae il numero riferito alla prova orale n. 18;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Andrea Alessia Nardo che nell'ordine:

- estrae il numero riferito alla prova orale n. 50;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell’uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Giusy Panepinto che nell’ordine:
- estrae il numero riferito alla prova orale n. 15;
- sottoscrive l’allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell’uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Giorgio Pashalidis che nell’ordine:
- estrae il numero riferito alla prova orale n. 8;
- sottoscrive l’allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell’uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 1 |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Chiara Pasquali che nell’ordine:
- estrae il numero riferito alla prova orale n. 3;
- sottoscrive l’allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell’uso delle apparecchiature e delle applicazioni informatiche più diffuse | 2 |

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|---|---|
| (fino a 2 punti): | |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Simone Maria Prestifilippo che nell'ordine:
- estrae il numero riferito alla prova orale n. 21;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Giuseppe Antonino Ragusa che nell'ordine:
- estrae il numero riferito alla prova orale n. 24;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

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|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 14 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **17** |

Segue il candidato Carlo Reina che nell'ordine:
- estrae il numero riferito alla prova orale n. 30;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 1 |
| Punteggio complessivo prova orale: | **18** |

Segue il candidato Andrea Rivela che nell'ordine:
- estrae il numero riferito alla prova orale n. 26;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)

- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 1 |
| Punteggio complessivo prova orale: | **18** |

Segue il candidato Federica Rivoli che nell'ordine:
- estrae il numero riferito alla prova orale n. 42;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 1 |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Clarissa Rizzo che nell'ordine:
- estrae il numero riferito alla prova orale n. 17;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Ludovica Rizzo che nell'ordine:
- estrae il numero riferito alla prova orale n. 22;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |

| | |
|---|---|
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Maria Ruggieri che nell'ordine:
- estrae il numero riferito alla prova orale n. 2;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Beatrice Sanfilippo che nell'ordine:
- estrae il numero riferito alla prova orale n. 45;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Enrico Santi Paolo Sciacca che nell'ordine:
- estrae il numero riferito alla prova orale n. 46;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Carla Spadaro che nell'ordine:

- estrae il numero riferito alla prova orale n. 39;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 15 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Eugenio Spagnolo che nell'ordine:

- estrae il numero riferito alla prova orale n. 49;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 15 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 1 |
| Punteggio complessivo prova orale: | **18** |

Segue il candidato Hosseini Alan Tammadon che nell'ordine:

- estrae il numero riferito alla prova orale n. 40;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 15 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 1 |
| Punteggio complessivo prova orale: | **17** |

Segue il candidato Vincenzo Tomasello che nell'ordine:

- estrae il numero riferito alla prova orale n. 44;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Francesco Giuseppe Tropea che nell'ordine:
- estrae il numero riferito alla prova orale n. 9;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Fabio Vignera che nell'ordine:
- estrae il numero riferito alla prova orale n. 32;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Luana Alaimo che nell'ordine:
- estrae il numero riferito alla prova orale n. 10;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Salvatore Ranieri Alù che nell'ordine:
- estrae il numero riferito alla prova orale n. 48;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Martina Bonsignore che nell'ordine:
- estrae il numero riferito alla prova orale n. 4;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Alba Borgese che nell'ordine:
- estrae il numero riferito alla prova orale n.16;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Silvia Giovanna Cicciarella che nell'ordine:
- estrae il numero riferito alla prova orale n. 14;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell’uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Antonino Cipolla che nell’ordine:
- estrae il numero riferito alla prova orale n. 37;
- sottoscrive l’allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell’uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Giuliana Cubisino che nell’ordine:
- estrae il numero riferito alla prova orale n. 19;
- sottoscrive l’allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell’uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Eugenia Di Fazio che nell’ordine:
- estrae il numero riferito alla prova orale n. 35;
- sottoscrive l’allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell’uso delle apparecchiature e delle applicazioni informatiche più diffuse | 2 |

| | |
|---|---|
| (fino a 2 punti): | |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Federica Di Giorgi che nell'ordine:
- estrae il numero riferito alla prova orale n. 6;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Chiara Di Maria che nell'ordine:
- estrae il numero riferito alla prova orale n. 29;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 15 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **19** |

Segue il candidato Laura Di Stefano che nell'ordine:
- estrae il numero riferito alla prova orale n. 13;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Giacomo Doria che nell'ordine:
- estrae il numero riferito alla prova orale n. 31;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)

- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Chiara Alfia Ferrara che nell'ordine:
- estrae il numero riferito alla prova orale n. 7;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 1 |
| Punteggio complessivo prova orale: | **18** |

Segue il candidato Sefora Fischetti che nell'ordine:
- estrae il numero riferito alla prova orale n. 11;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 2 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **20** |

Segue il candidato Agata Valentina Frazzetto che nell'ordine:
- estrae il numero riferito alla prova orale n. 23;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 14 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |

| | |
|---|---|
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **17** |

Segue il candidato Veronica Galioto che nell'ordine:
- estrae il numero riferito alla prova orale n. 34;
- sottoscrive l'allegato relativo alle domande estratte (allegato n. 3)
- quindi relaziona sugli argomenti estratti.

Ultimata la prova, la Commissione esaminatrice in base ai criteri stabili nel verbale n. 1, collegialmente ed all'unanimità assegna il seguente punteggio:

| | |
|---|---|
| Argomento inerente la disciplina a concorso (fino a 16 punti): | 16 |
| Lettura e traduzione brano in lingua inglese (fino a 2 punti): | 1 |
| Quesito volto ad accertare la conoscenza dell'uso delle apparecchiature e delle applicazioni informatiche più diffuse (fino a 2 punti): | 2 |
| Punteggio complessivo prova orale: | **19** |

Alle ore 17:30, ultimato lo svolgimento della prova, il Presidente legge i quesiti non estratti identificati con i numeri: 1,27,33, 43.

La Commissione quindi, sulla base delle risultanze come sopra specificatamente descritte, dichiara che hanno superato la prova orale n. 46 concorrenti esaminati e che hanno conseguito nella stessa una valutazione pari o superiore a quella di sufficienza di 14/20.

Al fine di informare i concorrenti sull'esito della terza ed ultima prova concorsuale, la Commissione elabora apposito report con i voti conseguiti dai candidati nella prova orale unitamente all'indicazione del superamento della stessa (**allegato 4)**.
La predetta tabella sarà pubblicata sull'apposita sezione relativa al concorso in questione del sito internet istituzionale aziendale, come comunicato ai candidati in occasione dell'effettuazione della prova in questione.

Alle ore 18:15 il Presidente dichiara chiusa la seduta ed aggiorna i lavori della Commissione per la formulazione delle graduatorie di merito previste dal bando.
Il presente verbale è letto, approvato e sottoscritto e le pagine che lo compongono sono siglate da tutti i membri.

Il Presidente Prof. Carlo Vancheri F.to Carlo Vancheri

Il Componente Dott. Carlo Santoriello F.to Carlo Santoriello

Il Componente Dott. Salvatore Bellofiore F.to Salvatore Bellofiore

Il Segretario Dott.ssa Maria Chiara Gagliano F.to M. Chiara Gagliano

Il presente documento firmato in originale è conservato agli atti del Settore Risorse Umane.

**Allegato n. 1 Verbale n. 7 del 02/07/2024**

**Azienda Ospedaliero Universitaria Policlinico**

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**Concorso pubblico, per titoli ed esami, per la copertura a tempo indeterminato di n. 3 posti di Dirigente Medico disciplina Malattie dell'Apparato Respiratorio.**

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1. Emottisi: eziologia ed approccio diagnostico
2. Ventilazione meccanica non invasiva: indicazioni e controindicazioni
3. OSAS: diagnosi
4. OSAS: trattamento
5. Diagnosi di asma bronchiale
6. Bronchiectasie
7. BPCO: diagnosi
8. Edema polmonare
9. BPCO: terapia
10. BPCO riacutizzata
11. Fibrosi polmonare idiopatica
12. Polmoniti nosocomiali
13. Tumore del polmone: diagnosi e stadiazione
14. Tumore del polmone: approccio terapeutico
15. Pneumotorace
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17. Versamento pleurico: diagnosi e trattamento
18. Dispnea: diagnosi differenziale
19. Insufficienza respiratoria acuta
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49. Polmonite organizzativa
50. Interstiziopatie polmonari fibrosanti

Il Presidente Prof. Carlo Vancheri F.to Carlo Vancheri

Il Componente Dott. Carlo Santoriello F.to Carlo Santoriello

Il Componente Dott. Salvatore Bellofiore F.to Salvatore Bellofiore

Il Segretario Dott.ssa Maria Chiara Gagliano F.to M. Chiara Gagliano

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**Allegato n. 1 Verbale n. 7 del 02/07/2024**

**Azienda Ospedaliero Universitaria Policlinico**

**"*G. Rodolico - San Marco*" CATANIA**

**Concorso pubblico, per titoli ed esami, per la copertura a tempo indeterminato di n. 3 posti di Dirigente Medico disciplina Malattie dell'Apparato Respiratorio.**

QUESITI DI INFORMATICA

1. Che cos'è l'applicativo Word e che utilizzo un utente può farne?
2. Che cos'è l'applicativo Power Point e che utilizzo un utente può farne?
3. Che cos'è l'applicativo Excel e che utilizzo un utente può farne?
4. Un "portale internet" o un "portale Intranet" sono la medesima cosa?
5. Cos'è Windows Media Player?
6. Cos'è la posta elettronica certificata (PEC)?
7. Che cos'è un "browser"?
8. Che cosa si intende per "antivirus"?
9. Cosa si intende per e-learning?
10. Che cosa si intende con il termine di "periferica"?
11. Se un collega tramite posta elettronica inoltra dei dati su un "foglio di lavoro elettronico" di che software ho bisogno per poterlo aprire ed eventualmente modificare o integrare?
12. Cos'è un motore di ricerca?
13. A cosa serve un backup?
14. La firma digitale.
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16. La funzione incolla.
17. La funzione taglia
18. La funzione cronologia.
19. La funzione dello scanner.
20. La casella di posta elettronica.
21. Le funzioni dell'hard disk.
22. Cos'è la telemedicina?
23. Cos'è una stampante multifunzione?
24. Differenza tra PEC e posta elettronica ordinaria.

25. Differenza tra File e Cartella.
26. Cos'è il desktop?
27. Cosa è Google Chrome?
28. In word è possibile attivare il controllo ortografico?
29. Che cosa è “Outlook Express”?
30. Cos’è per un PC la CPU?
31. Cosa è lo Spamming?
32. Cosa è la tecnologia Bluetooth?
33. La funzione filtro in Microsoft Excel.
34. Cos’è una connessione wireless?
35. La funzione del modem.
36. Cosa significa “zippare” un file.
37. Principali funzionalità di un database.
38. Cos’è il pendrive?
39. L’anteprima di stampa, funzioni e utilità.
40. Quali sono le principali funzionalità di una rete intranet?
41. Quali sono le principali funzionalità del software identificato come “foglio di calcolo”?
42. Cosa è l’hardware in una postazione informatica?
43. Differenza tra hardware e software.
44. Cos’è la RAM?
45. Che cosa si intende per “Firewall”?
46. Che cosa si intende con il termine “Attachment” ed in che ambito lo si può incontrare, e per quali finalità?
47. Se nell’ambito di una riunione si volessero presentare dei risultati con una presentazione al PC quale software risulterebbe più adeguato utilizzare e perché?
48. Cos’è il sistema operativo di un PC?
49. Cosa si intende per dispositivo tablet?
50. Cos’è il pdf?

Il Presidente Prof. Carlo Vancheri F.to Carlo Vancheri

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# Ventilator-induced coagulopathy in experimental *Streptococcus pneumoniae* pneumonia

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**ABSTRACT: Pneumonia, the main cause of acute lung injury, is characterised by a local pro-inflammatory response and coagulopathy. Mechanical ventilation (MV) is often required. However, MV can lead to additional injury: so-called ventilator-induced lung injury (VILI). Therefore, the current authors investigated the effect of VILI on alveolar fibrin turnover in *Streptococcus pneumoniae* pneumonia.**

**Pneumonia was induced in rats, followed 48 h later by either lung-protective MV (lower tidal volumes (LVT) and positive end-expiratory pressure (PEEP)) or MV causing VILI (high tidal volumes (HVT) and zero end-expiratory pressure (ZEEP)) for 3 h. Nonventilated pneumonia rats and healthy rats served as controls. Thrombin–antithrombin complexes (TATc), as a measure for coagulation, and plasminogen activator activity, as a measure of fibrinolysis, were determined in bronchoalveolar lavage fluid (BALF) and serum.**

**Pneumonia was characterised by local (BALF) activation of coagulation, resulting in elevated TATc levels and attenuation of fibrinolysis compared with healthy controls. LVT-PEEP did not influence alveolar coagulation or fibrinolysis. HVT-ZEEP did intensify the local procoagulant response: TATc levels rose significantly and levels of the main inhibitor of fibrinolysis, plasminogen activator inhibitor-1, increased significantly. HVT-ZEEP also resulted in systemic elevation of TATc compared with LVT-PEEP.**

**Mechanical ventilation causing ventilator-induced lung injury increases pulmonary coagulopathy in an animal model of *Streptococcus pneumoniae* pneumonia and results in systemic coagulopathy.**

**KEYWORDS: Acute respiratory distress syndrome, biotrauma, coagulation, mechanical ventilation, pneumonia**

Community-acquired pneumonia is the most frequent cause of acute lung injury (ALI) or its more severe form, acute respiratory distress syndrome (ARDS), often requiring mechanical ventilation (MV) [1]. Although MV provides essential life support, it can also worsen lung injury: so-called ventilator-induced lung injury (VILI). One large multicentre trial established the importance of VILI by demonstrating that ventilation with lower tidal volumes (*V*T) *versus* traditional *V*T (6 *versus* 12 mL·kg$^{-1}$) improves survival [2]. The spectrum of VILI also encompasses increases in pulmonary and systemic inflammatory mediators known as biotrauma [3–6], which has been linked to multiple organ failure [7].

Pulmonary inflammation associated with pneumonia is characterised by local generation of pro-inflammatory mediators and a pro-coagulant shift of the alveolar haemostatic balance [8]. The latter is the result of activation of coagulation on the one hand, which causes alveolar fibrin production, and attenuation of fibrin breakdown on the other [8, 9]. Disturbances in alveolar fibrin turnover have been demonstrated in patients with pneumonia [10, 11] and ALI/ARDS [11].

Recently, it was demonstrated that in models of VILI, local pulmonary fibrinolysis is suppressed during injurious mechanical ventilation known as ventilator-associated coagulopathy [12, 13]. However, the models used were iatrogenic in nature, either a single exposure to lipopolysaccharide [13] or fibrin deposits caused by human plasma without inflammation [12]. Furthermore, in neither of these models was systemic analysis performed. It is unknown whether mechanical

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# Evaluating the potential of IP-10 and MCP-2 as biomarkers for the diagnosis of tuberculosis

**M. Ruhwald*,#, T. Bodmer', C. Maier', M. Jepsen*, M.B. Haaland#, J. Eugen-Olsen# and P. Ravn#,+ on behalf of TBNET**

**ABSTRACT: The aim of the present study was to evaluate the potential of diagnostic tests based on interferon-γ inducible protein (IP)-10 and monocyte chemotactic protein (MCP)-2, and compare the performance with the QuantiFERON TB® Gold In-Tube (QFT-IT; Cellestis, Carnagie, Australia) test.**

**IP-10 and MCP-2 were determined in supernatants from whole blood stimulated with *Mycobacterium tuberculosis*-specific antigens. Samples were obtained from 80 patients with culture- and/or PCR-proven tuberculosis (TB), and 124 unexposed healthy controls: 86 high school students and 38 high school staff. IP-10 and MCP-2 test cut-offs were established based on receiver operating characteristic curve analysis.**

**TB patients produced significantly higher levels (median) of IP-10 (2158 pg·mL$^{-1}$) and MCP-2 (379 pg·mL$^{-1}$) compared with interferon (IFN)-γ (215 pg·mL$^{-1}$). The QFT-IT, IP-10 and MCP-2 tests detected 81, 83 and 71% of the TB patients; 0, 3 and 0% of the high school students and 0, 16 and 3% of the staff, respectively. Agreement between tests was high (>89%). By combining IP-10 and IFN-γ tests, the detection rate increased among TB patients to 90% without a significant increase in positive responders among the students.**

**In conclusion, interferon-γ inducible protein-10 and monocyte chemotactic protein-2 responses to *Mycobacterium tuberculosis*-specific antigens could be used to diagnose infection. Combining interferon-γ inducible protein-10 and interferon-γ may be a simple approach to increase the detection rate of the *Mycobacterium tuberculosis*-specific *in vitro* tests.**

**KEYWORDS: Diagnosis, interferon-γ, interferon-γ release assay, tuberculosis, whole blood**

A major breakthrough in the diagnosis of infection with *Mycobacterium tuberculosis* has been the development of *in vitro* assays that measure the production of interferon (IFN)-γ in response to stimulation with *M. tuberculosis*-specific antigens (IFN-γ release assay (IGRA) tests). The QuantiFERON TB® Gold In-Tube (QFT-IT; Cellestis, Carnagie, Australia) measures IFN-γ responses by ELISA following incubation of whole blood with region of difference (RD)1 and TB7.7 (Rv2654) antigens. The T-SPOT.TB® test (Oxford Immunotech, Abingdon, UK) measures the number of IFN-γ responding cells by the enzyme-linked immunosorbent spot method following incubation of purified peripheral blood mononuclear cells (PBMCs) with RD1 antigens.

The IGRA tests have been extensively examined and current evidence suggests that both tests have a low false-positive rate [1, 2]. Compared with the tuberculin skin test (TST), the IGRAs are better correlated with risk factors for infection with *M. tuberculosis* and do not give false-positive responses in bacille Calmette–Guerin (BCG)-vaccinated individuals [3–5]. Additionally, in patients with active tuberculosis (TB) and especially in immunocompromised individuals the IGRAs are more sensitive than the TST [6–10]. However, there is a concern that the detection rate is still suboptimal and the tests perform with more indeterminate results, and a lower detection rate in patients with severe TB and immunocompromised patients [7, 9–12].

For editorial comments see page 1428.
This article has supplementary material accessible from www.erj.ersjournals.com

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# Comparison of tuberculosis surveillance systems in low-incidence industrialised countries

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**ABSTRACT: The comparative analysis of National Tuberculosis Control Programmes (NTPs) in industrialised, low-tuberculosis-incidence countries is limited. Analysis of applied methods, function and accumulated experience contributes to improving global tuberculosis control.**

**A questionnaire addressing NTP surveillance infrastructure and characteristics was completed in 19 industrialised countries, with populations of >3 million and annual notified tuberculosis incidence rates of <16 cases per 100,000 population (2003 data).**

**All European countries surveyed adopted World Health Organization Collaborating Centre for the Surveillance of Tuberculosis in Europe (EuroTB) definitions. Surveillance information, which usually includes names, was transferred electronically to the national level in 17 out of the 19 countries. Surveillance systems capture process and social determinants. Case notification to the central level occurred within a median period of 7 days, independent of mandatory notification requirements. The mean completeness of tuberculosis case-reporting was estimated to be 93.5% (range 65–100%). Integration between HIV and tuberculosis registries was performed in two countries, and, in seven others, both databases were cross-matched periodically.**

**National Tuberculosis Control Programme function in industrialised low-incidence countries utilises well-established infrastructure and relies upon centralised operations. Approaches are consistent with current World Health Organization surveillance recommendations. The present study lays collaborative groundwork for additional multinational analyses for the enhancement of global tuberculosis surveillance, which may assist policy-makers in countries moving from medium to low rates of incidence.**

**KEYWORDS: Global health, National Tuberculosis Programme, surveillance, tuberculosis**

Tuberculosis (TB) control in industrialised countries varies substantially in its organisation, function and history. Consequently, it may be challenging to point to a set of discrete institutional components and label them the National Tuberculosis Control Programmes (NTPs). Each country has established NTP function, composed of an amalgamated network of organised public and private efforts, which has evolved in association with societal and economic trends in industrialised countries with what is now a low incidence of TB.

Surveillance performance, which provides notice of epidemiologically significant changes, is one of the fundamental public health activities necessary for the control and elimination of TB [1]. Since the 1950s, many countries have increasingly introduced organised surveillance activities at a national level. More recently, the World Health Organization (WHO) began comprehensive worldwide annual reporting of traditional TB surveillance data, as well as elements of programme management, which also include treatment outcomes and drug supply [2, 3].

Although surveillance performance in industrialised countries has developed independent of supranational guidance, most are consistent with the current WHO recommendations [3]. The definitions used for surveillance have also been endorsed by the International Union Against Tuberculosis and Lung Disease [4]. Since the 1990s, substantial efforts have been invested at the international level in developing recommendations and guidance for specialised areas in countries with high TB rates and technical matters related to policy development, including transition issues in countries shifting from low to middle income or from high to medium rates of incidence [5–11].

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# Pulmonary tuberculosis with acute respiratory failure

**Y.J. Kim*, K.M. Pack*, E. Jeong*, J.O. Na#, Y-M. Oh*, S.D. Lee*, W.S. Kim*, D.S. Kim*, W.D. Kim* and T.S. Shim***

**ABSTRACT: The aim of the present study was to evaluate the clinical characteristics, prognoses and predictors of mortality of patients with pulmonary tuberculosis (TB) with acute respiratory failure (ARF), and to investigate the adjunctive use of corticosteroids in such cases.**

**TB patients with ARF requiring mechanical ventilation (n=90) were enrolled retrospectively during 1989–2006. The patients were divided into two groups: tuberculous pneumonia (TBP; n=66), and miliary TB (MTB; n=24).**

**The TBP patients were older than the MTB patients (mean age 68.0 *versus* 54.5 yrs), and the mean±SD interval from hospital admission to start of anti-TB treatment was longer for the TBP than for the MTB group (5.0±7.0 *versus* 2.8±2.5 days). However, there was no difference in in-hospital mortality rate between the two groups (68.2 *versus* 58.3%). In the TBP patients, multivariate analysis showed that advanced age and shock unrelated to sepsis were associated with poor outcomes. Even though corticosteroid use was a predictor of survival in TBP patients, it was difficult to conclusively determine the efficacy of corticosteroids in TBP with ARF because of the retrospective study design.**

**The present study reveals the need for randomised controlled trials to clarify the role of corticosteroids as adjunctive therapy in the management of tuberculous pneumonia with acute respiratory failure.**

**KEYWORDS: Corticosteroids, mortality, prognostic factors, respiratory failure, tuberculosis**

Following decline since the mid-1950s, the incidence of tuberculosis (TB) has, since the mid-1990s, begun to increase in many countries. The control of this disease has been impeded by co-infection with HIV [1] and the emergence of multidrug-resistant TB [2]. Active pulmonary TB is a rare primary cause of acute respiratory failure (ARF) [3]; however, high mortality rates have recently been reported in patients with ARF arising from TB [4–6].

Corticosteroids are the most important physiological inhibitors of inflammation. Several randomised studies have shown efficacy and safety of corticosteroid treatment in patients with severe inflammatory conditions, such as catecholamine-dependent septic shock [7, 8], severe community-acquired pneumonia [9, 10] and early acute respiratory distress syndrome (ARDS) [11, 12]. With persistent unresolving ARDS, a beneficial effect of corticosteroid treatment was observed in some studies [13], but such improvements were not documented in others [14].

Corticosteroids have also been used as an adjunct in treating TB. The effective use of systemic corticosteroids in this regard is well-documented for several extrapulmonary forms of the disease, such as tuberculous meningitis [15] and tuberculous pericarditis [16]. Several studies have suggested that more rapid radiological resolution of pulmonary infiltrates and closure of cavities accompany steroid use; these effects may be more pronounced in patients with severe disease [17, 18]. However, corticosteroid use to modulate the harmful effects of severe inflammatory responses has not been prospectively investigated in patients with severe TB-induced ARF.

The present study was, therefore, conducted to: 1) evaluate the clinical characteristics of South Korean TB patients who develop ARF requiring mechanical ventilation; 2) determine the mortality rate and predictors of in-hospital mortality; and 3) investigate the status of adjuvant use of corticosteroids and the effect of such therapy on outcomes.

## MATERIALS AND METHODS

### *Patients*

The medical records of all relevant patients (aged >18 yrs) who had been admitted to the medical

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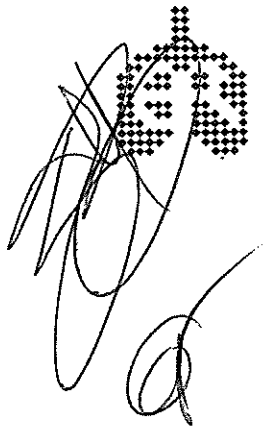
REVIEW

# Apoptosis in lung injury and fibrosis

**F. Drakopanagiotakis*, A. Xifteri*, V. Polychronopoulos* and D. Bouros#**



**ABSTRACT: Pulmonary fibrosis is characterised by fibroblast accumulation and alveolar epithelium denudation. Increased apoptosis of alveolar epithelial cells and decreased apoptosis of fibroblasts may play an important role in the pathogenesis of disease. Inflammatory cells can modulate apoptosis of other cell types, both by removal of apoptotic debris and by cytokine production, thus preserving a pro-fibrotic environment. In the present review, some of the mechanisms by which apoptosis may contribute to the pathogenesis of idiopathic pulmonary fibrosis are described.**

**KEYWORDS: Apoptosis, epithelium, fibroblast, mechanisms, pathogenesis, pulmonary fibrosis**

Idiopathic pulmonary fibrosis (IPF) is a chronic diffuse lung disease characterised by progressive deterioration in lung function ultimately leading to death. The histological pattern of IPF is usual interstitial pneumonia (UIP), described as the patchy presence of denuded alveolar epithelium, fibroblastic foci and distortion of lung architecture leading to honeycombing with minimal inflammation. It has been proposed that epithelium–fibroblast interactions may lead to alveolar cell loss and the initiation of the fibrotic process [1].

Apoptosis, or programmed cell death, is an important physiological process for the development and the maintenance of tissue homeostasis, ensuring a balance between cellular proliferation and turnover in nearly all tissue types.

Apoptosis may participate in the development of lung disease *via* three different mechanisms: 1) increased apoptosis of epithelial cells leading to inefficient re-epithelialisation [2]; 2) resistance to apoptosis of fibroblasts leading to increased fibrosis [2]; and 3) ineffective removal of apoptotic cells (efferocytosis) by granulocytes sustaining a persistent inflammatory state [3].

Although significant progress has been made with regard to the understanding of the mechanisms involved in the development of pulmonary fibrosis, the pathogenesis of the disease is not yet clear. An important part of the present knowledge has arisen from animal models, such as the bleomycin-induced pulmonary fibrosis model. However, this model has certain limitations, specifically the differences in chronicity and pathogenesis between this model and IPF. In the murine bleomycin model, acute alveolitis develops with significant inflammation followed by fibrosis in a short period of time, unlike the indolent fibrosis and minimal inflammation seen in human IPF [4].

The aim of the present review is to characterise the importance of apoptosis as a potential pathogenic mechanism in the development of pulmonary fibrosis and its relationship with other pathogenic processes.

## MECHANISMS OF APOPTOSIS

Apoptotic cells undergo various morphological changes, including cell shrinkage, membrane blebbing, cleavage of chromosomal DNA and the release of the membrane-bound apoptotic bodies. Apoptosis mechanisms involve: 1) the initiation phase, during which apoptotic stimuli lead to caspase activation; and 2) the execution phase, during which caspases induce cell death.

The caspase cascade can be activated by different pathways (fig. 1) [5].

### *The extrinsic or death receptor pathway*

The extrinsic or death receptor pathway involves the activation of death receptors present in the cell membrane, such as Fas and tumour necrosis factor (TNF) receptor 1. Connection of the death ligand to its death receptor leads to activation of an adaptor protein called activated death domain and the subsequent activation of procaspase-8 or -10. Activated caspases induce apoptosis. The extrinsic pathway can be inhibited by at least three mechanisms: 1) FLIP (Fas-activated death domain (FADD)-like interleukin-1 converting enzyme (FLICE)-like inhibitor of apoptosis protein), which binds to procaspase-8 without

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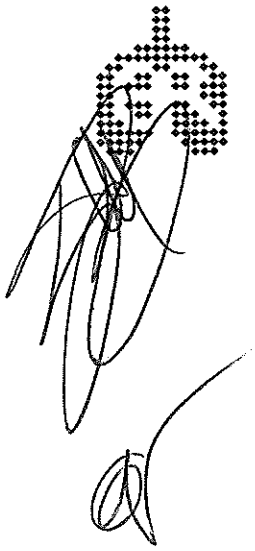

**SERIES "HYPOXIA: ERS LUNG SCIENCE CONFERENCE"**
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# Regulation of hypoxic pulmonary vasoconstriction: basic mechanisms

**N. Sommer*, A. Dietrich#, R.T. Schermuly*, H.A. Ghofrani*, T. Gudermann#, R. Schulz*, W. Seeger*, F. Grimminger* and N. Weissmann***

**ABSTRACT: Hypoxic pulmonary vasoconstriction (HPV), also known as the von Euler–Liljestrand mechanism, is a physiological response to alveolar hypoxia which distributes pulmonary capillary blood flow to alveolar areas of high oxygen partial pressure.**

**Impairment of this mechanism may result in hypoxaemia. Under conditions of chronic hypoxia generalised vasoconstriction of the pulmonary vasculature in concert with hypoxia-induced vascular remodelling leads to pulmonary hypertension. Although the principle of HPV was recognised decades ago, its exact pathway still remains elusive. Neither the oxygen sensing process nor the exact pathway underlying HPV is fully deciphered yet. The effector pathway is suggested to include L-type calcium channels, nonspecific cation channels and voltage-dependent potassium channels, whereas mitochondria and nicotinamide adenine dinucleotide phosphate oxidases are discussed as oxygen sensors. Reactive oxygen species, redox couples and adenosine monophosphate-activated kinases are under investigation as mediators of hypoxic pulmonary vasoconstriction. Moreover, the role of calcium sensitisation, intracellular calcium stores and direction of change of reactive oxygen species is still under debate.**

**In this context the present article focuses on the basic mechanisms of hypoxic pulmonary vasoconstriction and also outlines differences in current concepts that have been suggested for the regulation of hypoxic pulmonary vasoconstriction.**

**KEYWORDS: Hypoxia, hypoxic pulmonary vasoconstriction, lung, oxygen, oxygen sensing**

Hypoxic pulmonary vasoconstriction (HPV) is a physiological self-regulatory response to alveolar hypoxia that distributes pulmonary capillary blood flow to areas of high oxygen availability. This principle, also known as the von Euler–Liljestrand mechanism, thereby optimises gas exchange at the blood–air interface [1, 2].

Impairment of this mechanism during pathological situations in lung or systemic disease (for example, adult respiratory distress syndrome [3] or hepatopulmonary syndrome [4]) or during anaesthesia [5], may result in insufficient oxygenation of arterial blood and poor oxygen supply to the body. Chronic hypoxia, as it occurs at high altitude or during respiratory diseases (including chronic obstructive pulmonary disease, sleep apnoea, fibrosis, failure of ventilation due to neurological diseases), may lead to general vasoconstriction of the pulmonary vasculature inducing vascular remodelling processes with subsequent right heart hypertrophy and cor pulmonale.

Due to the opposite functions of lung vessels and systemic vessels, collecting and distributing oxygen, respectively, different reactions to hypoxia have developed. Whereas most systemic vessels of adult organisms dilate during hypoxia, pulmonary vessels constrict. During embryonic development lung vessels exhibit pronounced

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CASE STUDY

# Bronchial fistulae in ARDS patients: management with an extracorporeal lung assist device

**M. Hommel*, M. Deja*, V. von Dossow*, K. Diemel#, C. Heidenhain", C. Spies* and S. Weber-Carstens***

ABSTRACT: **Patients with bronchial tree lesions feature, in particular, a high risk for developing bronchial fistulae after surgical repair when the clinical situation is complicated by acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) and mechanical ventilation is needed. The current authors hypothesised that extracorporeal carbon dioxide removal would significantly decrease inspiratory airway pressures, thus promoting the protection of surgical bronchial reconstruction.**

**Four patients were studied after surgical reconstruction of bronchial fistulae in whom ALI/ARDS developed and mechanical ventilation with positive end-expiratory pressure was required. Gas exchange, tidal volumes, airway pressures, respiratory frequency, vasopressor and sedation requirements were analysed before and after initiation of a pumpless extracorporeal lung assist device (pECLA; NovaLung®, Talheim, Germany). Initiation of pECLA treatment enabled a reduction of inspiratory plateau airway pressures from 32.4 to 28.6 cm$H_2O$ (3.2 to 2.8 kPa), effectively treated hypercapnia (from 73.6 to 53.4 mmHg (9.8 to 7.1 kPa)) and abolished respiratory acidosis (from pH 7.24 to 7.41). All patients survived and were discharged to rehabilitation clinics.**

**In patients after surgical bronchial reconstruction that was complicated by acute lung injury/acute respiratory distress syndrome, use of pumpless extracorporeal carbon dioxide removal was safe and efficient. Initiation of a pumpless extracorporeal lung assist device enabled a less invasive ventilator management, which may have contributed to healing of surgical bronchial repair.**

KEYWORDS: **Acute respiratory distress syndrome, bronchial fistula, extracorporeal carbon dioxide removal, mechanical ventilation, pumpless extracorporeal lung assist device**

Ruptures or fistulae of the bronchial tree after pulmonary surgery, *e.g.* lobectomy, have been reported with an incidence of 1.5–28% [1]. Inflammatory diseases seem to be an important risk factor for the development of bronchial fistulae (7.8%), especially in mechanically ventilated patients [1]. Positive pressure ventilation results in a considerable risk, in patients with bronchopleural fistula, of perpetuating the bronchial fistula and compromising surgical repair. Mortality has been reported as high as 67% in patients with bronchial fistulae receiving mechanical ventilation [1]. Mechanical ventilation applying positive airway pressures, therefore, should be avoided whenever possible, and early extubation is a major goal in perioperative therapy.

However the treatment of ruptures or fistulae of the bronchial tree remains a challenging surgical and intensive care medical problem. In the present case series, four patients were studied after surgical reconstruction of bronchial fistulae whose clinical course was complicated by acute lung injury/acute respiratory distress syndrome (ARDS) requiring high positive end-expiratory (PEEP) levels [2] and advanced ventilator support. It was hypothesised

For editorial comments see page 1431.

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# *Pseudomonas aeruginosa* transmission is infrequent in New Zealand cystic fibrosis clinics

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ABSTRACT: ***Pseudomonas aeruginosa* is an important pathogen in cystic fibrosis (CF). Although most patients harbour unique *P. aeruginosa* isolates, some clinics report patients sharing common strains. The overall importance of person-to-person transmission in *P. aeruginosa* acquisition and whether routine patient segregation is necessary remains uncertain. The present authors therefore investigated the extent of *P. aeruginosa* transmission in New Zealand CF clinics.**

**New Zealand's seven major CF centres were assessed, combining epidemiological data with computer-assisted *SalI* DNA fingerprinting of 496 isolates from 102 patients.**

**One cluster of related isolates was significantly more prevalent in the largest clinic than expected by chance. The seven patients with isolates belonging to this cluster had more contact with each other than the remaining patients attending this centre. No other convincing evidence of transmission was found in any of the other smaller clinics. Three *P. aeruginosa* strains believed to be transmissible between patients in Australian and British CF clinics are present in New Zealand, but there was no definite evidence they had spread.**

***Pseudomonas aeruginosa* transmission is currently infrequent in New Zealand cystic fibrosis clinics. This situation could change rapidly and ongoing surveillance is required. The current results confirm that computer-assisted *SalI* DNA fingerprinting is ideally suited for such surveillance.**

**KEYWORDS: Cystic fibrosis, DNA typing, *Pseudomonas aeruginosa*, transmission**

Once *Pseudomonas aeruginosa* is established within the lungs of patients with cystic fibrosis (CF) there is an accelerated decline in pulmonary function, quality of life and life-expectancy [1]. Most CF patients acquire *P. aeruginosa* strains from environmental sources [2]. However, siblings are often infected with indistinguishable clones suggesting person-to-person transmission instead of common environmental exposure [3]. Furthermore, in several European, English and Australian CF clinics, many patients share a common strain [2, 4–7]. Some strains appear in several clinics [8, 9], others superinfect patients already chronically colonised with unrelated *P. aeruginosa* isolates [10], while some are associated with worse outcomes and increased treatment costs [6, 7, 11–13]. In contrast, others have found only small clusters of genetically similar isolates from CF patients lacking geographic or temporal relationships other than attending the same clinic [14–16]. Rather than from cross-infection, such clusters could be due to common environmental sources or limited discriminatory power of typing methods [17].

Consequently, *P. aeruginosa* transmission between CF patients may occur, but only after prolonged close contact, as in siblings, or from small numbers of strains with heightened potential for transmission. Nonetheless, British and, more recently, Australian CF Trust infection control guidelines and the European consensus report recommend that all CF patients with *P. aeruginosa* be segregated to reduce cross-infection [18–20]. Centres in Australia and Europe that implemented these recommendations have been successful at restricting potentially transmissible strains [21, 22]. However,

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# ExoU-induced procoagulant activity in *Pseudomonas aeruginosa*-infected airway cells

**M.C. Plotkowski, L.F.P. Feliciano, G.B.S. Machado, L.G. Cunha Jr, C. Freitas, A.M. Saliba and M.C. de Assis**

ABSTRACT: **The present study addressed the question whether ExoU, a *Pseudomonas aeruginosa* toxin with phospholipase A2 (PLA2) activity, may induce airway epithelial cells to overexpress tissue factor (TF) and exhibit a procoagulant phenotype.**

**Cells from the human bronchial epithelial BEAS-2B line were infected with an ExoU-producing *P. aeruginosa* strain, pre-treated or not with the cytosolic PLA2 inhibitor methylarachidonyl fluorophosphate (MAFP), or with two ExoU-deficient mutants. Control noninfected and infected cells were assessed for the expression of: 1) TF mRNA by RT-PCR; 2) cell-associated TF by enzyme immunoassay and flow cytometry; 3) procoagulant activity by a colorimetric assay; and 4) microparticle-associated TF by flow cytometry. An enzyme immunoassay was also used to assess cell-associated TF in lung extracts from mice infected intratracheally with ExoU-producing and -deficient bacteria.**

**Cells infected with the wild-type bacteria had higher levels of TF mRNA, cell-associated TF expression, procoagulant activity and released microparticle-associated TF than cells infected with the mutants. Bacterial treatment with MAFP significantly reduced the expression of TF by infected cells. Lung samples from mice infected with the wild-type bacteria exhibited higher levels of cell-associated TF and procoagulant activity.**

**The present results demonstrate that ExoU may contribute to the pathogenesis of lung injury by inducing a tissue factor-dependent procoagulant activity in airway epithelial cells.**

KEYWORDS: **ExoU, lung injury, procoagulant activity, *Pseudomonas aeruginosa*, sepsis, tissue factor**

*Pseudomonas aeruginosa* is one of the leading causes of Gram-negative nosocomial pneumonia. *P. aeruginosa* hospital-acquired pneumonia often results in sepsis, a severe clinical syndrome characterised by a generalised activation of inflammation and coagulation pathways.

The lungs are among the most frequently affected organs during sepsis [1], and characteristically show fibrin deposition in alveolar and interstitial compartments [2]. Besides compromising the lung gas-exchange barrier, alveolar clotting processes are harmful because neutrophils and fibroblasts may be activated further by thrombin and fibrin degradation products, contributing to further tissue damage. Moreover, surfactant components may be incorporated into polymerising fibrin with subsequent loss of surface activity and alveolar instability [3]. However, the mechanisms that control fibrin deposition in patient airways remain poorly understood.

Tissue factor (TF; CD142), the major physiological initiator of the coagulation cascade, is an integral membrane protein expressed on a number of cells not in direct contact with blood. However, in both monocytes and endothelial cells, TF can be readly up-regulated by proinflammatory cytokines, bacterial lipopolysaccharide (LPS) and many other proinflammatory stimuli [4], giving these cells a prothrombotic phenotype. TF is fully functional when expressed on cell surfaces and binds factor VII, supporting its allosterical activation to factor VIIa. The enzymatic TF–VIIa complex then initiates the downstream clotting events that culminate in the conversion of prothrombin to thrombin. Thrombin proteolytically cleaves fibrinogen, yielding fibrin monomers that polymerise into a stable clot required for physiological haemostasis.

TF is also present in human tissues with large procoagulant activity, such as brain and placenta, as well as in multiple lung cells, including

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# Interferon-β augments eosinophil adhesion-inducing activity of endothelial cells

**T. Kobayashi, Y. Takaku, A. Yokote, H. Miyazawa, T. Soma, K. Hagiwara, M. Kanazawa and M. Nagata**

**ABSTRACT: Viral infections induce exacerbations of asthma. One of the earliest host responses to viral infections is the production of innate cytokines including type I interferons (IFNs), such as IFN-β, which may act to modify airway inflammation. The objective of the present study was to investigate whether IFN-β modifies the eosinophil adhesion-inducing activity of endothelial cells.**

**Human umbilical vein endothelial cells (HUVECs) were stimulated with IFN-β for 24 h in the presence or absence of tumour necrosis factor (TNF)-α. Eosinophils were isolated from the peripheral blood of healthy volunteers. The ability of the IFN-β-stimulated HUVEC monolayers to induce eosinophil adhesion was assessed according to the eosinophil peroxidase assay.**

**Eosinophil adhesion to HUVECs was significantly augmented by IFN-β in the presence of TNF-α but not in its absence. The augmented adhesion was inhibited by anti-$\alpha_4$ integrin monoclonal antibody (mAb) or anti-$\beta_2$ integrin mAb. IFN-β significantly enhanced the expression of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 on HUVECs in the presence of TNF-α.**

**Interferon-β can augment the adhesiveness of endothelial cells to eosinophils, mainly through the expression of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1. This action of interferon-β may contribute to the intensification of airway inflammation in asthma that is associated with exacerbations induced by viral infections.**

**KEYWORDS: Asthma, endothelial cells, eosinophilic airway inflammation, viral infection**

Acute respiratory infections commonly precede asthma exacerbations in both children and adults [1–3]. The majority of episodic exacerbations of asthma are induced by viral respiratory infections, in particular rhinovirus infections [4]. The mechanism by which viral respiratory infections exacerbate asthma is a complex process that may be regulated by the enhanced production of cytokines, chemokines and other classes of inflammatory molecules [4, 5]. An effective antiviral immune response requires the early clearance of viruses and the appropriate termination thereof, to minimise concomitant immunopathology and tissue damage. One of the earliest host responses to viral infections is the production of initial innate cytokines. These cytokines include type I interferons (IFNs) such as IFN-β [6, 7]. WARK *et al.* [7] recently reported that respiratory epithelial cells from asthmatics have a lower IFN-β-producing ability that is associated with a reduced ability to clear viruses. Since IFNs have a variety of pro-inflammatory actions on inflammatory cells, including eosinophils, epithelial cells and endothelial cells [8–12], it is theoretically conceivable that these cytokines may modify and aggravate the inflammatory status of airway diseases, including asthma, during or after viral infection.

Eosinophils are inflammatory cells predominantly found in the airways of asthmatic patients and are likely to contribute to the pathogenesis of asthma through the production of a variety of mediators including cysteinyl (cys) leukotriene (LT) and transforming growth factor-β [11–14]. Although neutrophils play central roles in asthma exacerbations induced by viral respiratory infections, clinical data support the involvement of eosinophils in virus-induced exacerbations and increased airway hyperresponsiveness in asthmatic patients [15–17]. In atopic asthmatics, for example, experimental infections with rhinovirus (RV)16 increased epithelial eosinophil counts; this increase appeared to persist up to convalescence [15]. In asthmatic patients with confirmed viral infection, sputum showed high eosinophilic cationic protein (ECP) levels [16]. In atopic mild asthmatics, increased airway hyperresponsiveness to histamine was correlated significantly with an increase in ECP levels and with changes in eosinophil levels in induced

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# Changes in lung volumes and airway responsiveness following haematopoietic stem cell transplantation

**G. Barisione*, A. Bacigalupo#, E. Crimi', M.T. Van Lint#, T. Lamparelli# and V. Brusasco'**

**ABSTRACT: Changes in lung volume occur following haematopoietic stem cell transplantation (HSCT); airway hyperresponsiveness was occasionally reported, without mechanistic explanation. The present authors studied 17 patients by standard methacholine (MCh) challenge before and then 3 and 12 months after HSCT (n=16 and n=13, respectively). Another 6 patients were challenged before and 3 months after HSCT using a modified challenge to investigate the effect of deep inhalations.**

**No patient developed bronchiolitis obliterans or bronchiolitis obliterans organising pneumonia. At 3 months, forced vital capacity (FVC) was significantly reduced by 0.33±0.55 L, forced expiratory volume in one second ($FEV_1$) by 0.31±0.50 L, total lung capacity (TLC) by 0.39±0.37 L and single-breath diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) by 15±12%. At 12 months, TLC decreased by 0.43±0.36 L and $D_{L,CO}$ by 8±8%. With standard challenge, no significant changes in $FEV_1$ response to MCh were observed after HSCT but FVC decreased significantly less after HSCT compared with prior to HSCT, suggesting less air trapping. With modified challenge, deep inhalations reversed the MCh-induced decrease in partial expiratory flow more after HSCT compared with before HSCT and this correlated with TLC decrements.**

**In conclusion, an increase in airway responsiveness is unlikely after haematopoietic stem cell transplantation, at least in patients without pulmonary complications, and mechanisms opposing airway narrowing may blunt the bronchoconstrictor response.**

**KEYWORDS: Deep inhalations, haematological malignancies, lung restriction, methacholine**

Patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT) are susceptible to developing severe pulmonary complications [1, 2], including bronchiolitis obliterans and bronchiolitis obliterans organising pneumonia (BOOP). The former has a reported incidence of 0–48% and results in a purely obstructive functional abnormality at late onset (around 1 yr post-HSCT), whereas the latter is rare (<2%) and characterised by an early (usually within the first 100 days) restrictive abnormality associated with a reduction of single-breath diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) [3].

Prospective studies of patients undergoing HSCT have shown that lung function changes also occur independently of the development of BOOP or bronchiolitis obliterans [4–6]. Collectively, these studies have shown consistent reductions of forced vital capacity (FVC), forced expiratory volume in one second ($FEV_1$), total lung capacity (TLC) and $D_{L,CO}$, thus suggesting the development of a restrictive disorder possibly due to the concomitant treatments. An increase in airway responsiveness to methacholine (MCh) was occasionally reported either before [7, 8] or after [8] HSCT. The clinical relevance of airway hyperresponsiveness in transplant recipients may vary depending on its underlying mechanism. In lung transplant recipients it occurs frequently [9–12] and has been regarded as a risk factor for the development of bronchiolitis obliterans [11, 12], possibly reflecting an early derangement of airway mechanics. Alternatively, airway hyperresponsiveness may be the consequence of breathing at low lung volume, thus reflecting a reduced elastic load on a normally behaving airway smooth muscle.

The present prospective study aimed to investigate whether changes in airway responsiveness occur in patients undergoing HSCT. Moreover, as bronchial responsiveness is the result of both

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# Predicting worsening asthma control following the common cold

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ABSTRACT: **The asthmatic response to the common cold is highly variable, and early characteristics that predict worsening of asthma control following a cold have not been identified.**

**In this prospective multicentric cohort study of 413 adult subjects with asthma, the mini-Asthma Control Questionnaire (mini-ACQ) was used to quantify changes in asthma control and the Wisconsin Upper Respiratory Symptom Survey-21 (WURSS-21) to measure cold severity. Univariate and multivariable models were used to examine demographic, physiological, serological and cold-related characteristics for their relationship to changes in asthma control following a cold.**

**Clinically significant worsening of asthma control was observed following a cold (mean±SD increase in mini-ACQ score of 0.69±0.93). Univariate analysis demonstrated that season, centre location, cold duration and cold severity measurements were all associated with a change in asthma control. Multivariable analysis of the covariates available within the first 2 days of cold onset revealed that the day 2 and cumulative sum of day 1 and 2 WURSS-21 scores were significant predictors of the subsequent changes in asthma control.**

**In asthmatic subjects, cold severity within the first 2 days can be used to predict subsequent changes in asthma control. This information may help clinicians prevent deterioration in asthma control following a cold.**

KEYWORDS: **Asthma, asthma control, common cold**

Respiratory tract infections (including the common cold) have been associated with increased asthma symptoms, exacerbations and hospitalisations [1–4]. Recent prospective longitudinal cohort studies in asthmatic adults have also documented an association between respiratory tract infection and worsening asthma symptoms, decline in lung function and asthma exacerbations [5–9]. For each of these end-points, there was a highly variable clinical response to respiratory tract infection. In the controlled research setting of an experimental rhinoviral infection, asthmatic subjects also demonstrated a variable clinical, pathological and physiological response [10–18]. Despite documentation of an acute upper respiratory infection, asthma symptoms ranged from none to severe. Although these studies observed a highly variable post-cold clinical course, none attempted to identify patient or cold episode characteristics that predict a subsequent change in asthma control. Given the current emphasis on measuring asthma control in the National Asthma Education and Prevention Program Expert Panel Report 3 guidelines [2], improved understanding of the effect of a cold on asthma control is needed.

The Post-cold Asthma Control and Exacerbation (PAX) study was designed to identify early characteristics that predict subsequent worsening of asthma control following a cold. This was a multicentric prospective cohort study in adult subjects with mild-to-moderate persistent asthma aimed at defining the prospective incidence of natural colds in asthmatics and identifying early predictors of the changes in asthma control following a cold. It was postulated that patient

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# Physical training does not increase allergic inflammation in asthmatic children

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ABSTRACT: **The effects of a 3-month physical training programme on airway inflammation and clinical outcomes were studied in school-aged children with asthma.**

**Subjects with persistent allergic asthma (aged 12.7±3.4 yrs; n=34) were randomly allocated into training and control groups. Exercise consisted of twice-weekly 50-min sessions for 12 weeks. Inflammation was assessed by levels of exhaled nitric oxide, blood eosinophils, eosinophil cationic protein, C-reactive protein, and total and mite-specific immunoglobulin (Ig)E. Lung volumes and bronchial responsiveness to methacholine were determined. The Paediatric Asthma Quality of Life Questionnaire and Paediatric Asthma Caregiver's Quality of Life Questionnaire were used to evaluate activity restrictions, symptoms and emotional stress. The efficacy of the training was assessed by accelerometry.**

**Following the programme, the exercise group spent twice as much time as the controls undertaking moderate-to-vigorous activities. No differences in changes were seen between groups for asthma outcomes. However, total IgE decreased more in the exercise group, as did mite-specific IgE.**

**Training did not increase inflammation in children with persistent asthma, and may have decreased both total and allergen-specific immunoglobulin E levels. It is concluded that there is no reason to discourage asthmatic children with controlled disease to exercise.**

KEYWORDS: **Asthma, exhaled nitric oxide, physical activity, quality of life, randomised controlled trial**

The increase in the prevalence of asthma observed in most developed countries has been accompanied by important changes in lifestyle [1]. Reduced physical activity has been associated with increased asthma prevalence [2–4], and high levels of physical activity have been suggested to prevent disease progress [5]. Physical training may reduce breathlessness and asthma symptoms by strengthening respiratory muscles and decreasing ventilatory rate during exercise. Training programmes in asthma have not, however, shown any improvement in lung function in controlled trials [5–12]. The effects on airway inflammation are largely unknown.

Heavy physical activity has also been related to asthma occurrence and exacerbation. In elite athletes, asthma is diagnosed more frequently than in the general population [13]. This has been attributed to airway inflammation and increased bronchial responsiveness induced by high-intensity long-term exercise, such as competitive swimming or long-distance running. Asthma symptoms may attenuate after discontinuing training and competition [14, 15]. Atopy and type of sport appear to be the two major risk factors, with atopic long-distance runners having the highest risk of asthma compared to nonatopic non-athletes [16].

The effects of a 3-month physical training programme on airway inflammation and clinical outcomes were studied in school-aged children with persistent asthma. The aim of the present study was to determine a rationale for exercise and sporting guidance for children and their parents.

## METHODS

### *Patient selection*

Atopic school-aged children with controlled asthma, treated with a small-to-moderate dose of inhaled corticosteroids (ICSs) for a period of ⩾1 yr and followed in the outpatient clinic of

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# Antenatal infection in the rabbit impairs post-natal growth and lung alveolarisation

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ABSTRACT: **Clinical and experimental studies indicate an association between chorioamnionitis and bronchopulmonary dysplasia in preterm infants. The present authors hypothesised that, in the rabbit, antenatal infection may impair lung development after birth, despite effective maternal antibiotic therapy.**

**Pregnant rabbits received an intra-uterine inoculation of $10^3$ *Escherichia coli* colony forming units or vehicle at the end of gestation (day 29). Intravenous ceftriaxone therapy was initiated 8 h after inoculation for a period of 8 days. Pups born between 60 and 84 h after inoculation were kept with their mother until sacrifice on days 0, 1, 5, 8 and 15.**

**Blood cultures from antenatally infected animals were sterile at birth. Postnatal growth was significantly impaired by day 8. Lung morphometry showed a significant decrease of alveolar surface density and interstitial density, with a significant increase of alveolar airspace volume, indicating impaired alveolarisation for the first 2 weeks of postnatal life. Inflammatory and apoptotic processes were not detected in the lung at birth or subsequently.**

**Intra-uterine infection in rabbits is, therefore, responsible for concomitant postnatal growth retardation and abnormal pulmonary development despite early and effective antenatal antibiotic therapy. This may constitute an alternative model to study the consequences of antenatal infection on postnatal growth and lung development.**

KEYWORDS: **Bacterial infections, bronchopulmonary dysplasia**

Despite recent major advances in the management of premature infants, including surfactant administration and noninvasive mechanical ventilation, most immature neonates, often weighing less than 1,000 g at birth, are prone to develop lung sequelae corresponding to bronchopulmonary dysplasia (BPD) [1]. BPD is mainly related to arrested lung development, including decreased expression of key factors regulating alveolar and vascular development [2, 3], and marked reduction in total alveolar number [4]. Numerous risk factors have been identified, including mechanical ventilation, oxygen therapy, patent ductus arteriosus and nosocomial infection [5]. However, there is growing evidence that antenatal infection may play a crucial role in the pathogenesis of BPD [6]. WATTERBERG *et al.* [7] reported that 80% of infants without respiratory distress syndrome, who nevertheless developed BPD, were born in a context of chorioamnionitis. Moreover, maternal stage of chorioamnionitis was correlated with severity of BPD [8]. Experimental models have highlighted the role of inflammation induced by intra-amniotic endotoxin in altered lung development in fetal sheep [9, 10] or rats [11]. However, these models of selective amniotic fluid inflammation are quite different from the characteristic features associated with the pathophysiology of chorioamnionitis, which consist of active bacterial infection.

In the present study, a model of intra-uterine infection in the rabbit was used to evaluate the effects of infection on neonatal lung development. This model of *Escherichia coli* chorioamnionitis represents an active infection with relevance to human pathology, as *E. coli* is involved in numerous neonatal infections [12, 13]. The impact of intra-uterine infection on newborn lung development was evaluated by studying lung morphometry and cell death, and the impact on inflammation status was studied by inflammatory cell counts and interleukin (IL)-6 determination in bronchoalveolar lavage (BAL) fluid from birth until 2 weeks of postnatal life.

## METHODS

### *Antenatal infection*

The study was conducted in pregnant and newborn New Zealand rabbits, with the RS218

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# The responsiveness and validity of the CAMPHOR Utility Index

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**ABSTRACT: The aim of the present study was to validate and determine the mininal important difference (MID) and responsiveness of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) Utility Index, a new tool enabling cost utility analyses.**

**CAMPHOR, 6-min walking test (6MWT) and New York Heart Association (NYHA) data for 869 pulmonary hypertension patients (545 (63%) female; mean±SD age 56.6±15.4 yrs) from three centres were analysed. Utility was correlated with 6MWT data and calculated by NYHA class to assess validity. Effect sizes were calculated for those with two CAMPHOR assessments. Distribution and anchor-based MIDs were calculated. Analyses were carried out in patients receiving bosentan in order to determine whether or not those remaining in NYHA class III following treatment improved.**

**The Utility Index distinguished between adjacent NYHA classes and correlated with 6MWT results. CAMPHOR subscales and utility were as responsive as the 6MWT (effect sizes ranged 0.31–0.69 for the CAMPHOR and 0.16–0.34 for the 6MWT). The within-group MID for the Utility Index was estimated to be ~0.09. Patients remaining in NYHA class III experienced, on average, a significant improvement (CAMPHOR Utility Index and functioning), which exceeded the MID.**

**The CAMPHOR Utility Index is valid and responsive to change. Patients can experience significant and important improvements even if they do not improve on the basis of traditional outcomes, such as NYHA functional class.**

**KEYWORDS: Bosentan, Cambridge Pulmonary Hypertension Outcome Review, pulmonary hypertension, quality of life, responsiveness, utility**

Pulmonary hypertension (PH) is a rare disease, affecting 2–5 per million population annually [1]. It is characterised by elevated pulmonary arterial pressure and pulmonary vascular resistance, which ultimately result in right heart failure and death [1, 2]. PH most commonly arises as a result of underlying cardiopulmonary disease, but may also be a consequence of pulmonary thromboembolic disease or disease of the pulmonary microcirculation [3].

Symptoms include dyspnoea, fatigue, palpitations, peripheral oedema, chest pain and syncope [2]. Available treatments include intravenous epoprostenol, subcutaneous and intravenous treprostinil and inhaled iloprost, and oral therapies, such as endothelin receptor antagonists (bosentan, sitaxsentan and ambrisentan) and the phosphodiesterase type 5 inhibitor sildenafil [4, 5]. However, the currently available treatments (with the exception of pulmonary endarterectomy for thromboembolic PH) do not cure the disease [6]. The current aim of therapy is to reduce pulmonary arterial pressure, improve right heart function, improve exercise capacity and, ultimately, to lengthen survival time and improve quality of life (QoL).

Given the high cost of PH treatments (for example, epoprostenol costs £130–390 (GBP sterling) daily in the UK, and bosentan and sitaxentan each cost £55 daily in the UK [7]), there is a need to establish that the treatments are cost-effective. This necessitates a cost–utility analysis in which the cost of treatment is related to the benefit gained in terms of a parameter that expresses the quantity of life and QoL, the quality-adjusted life year (QALY). The QALY requires information relating to patients' preferences expressed in terms of utility, which is generally expressed as a value between 1 (representing perfect health) and 0 (death). To date, utility in PH populations, as in most other diseases, has been derived by asking patients to complete generic questionnaires, such as the European quality of life five-dimension (EQ-5D) questionnaire [8], which provide a utility score. Evidence suggests that disease-specific utility

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# Increased hyaluronic acid content in idiopathic pulmonary arterial hypertension

**E. Papakonstantinou*,[c], F.M. Kouri#,[c], G. Karakiulakis*, I. Klagas* and O. Eickelberg#**

**ABSTRACT: Idiopathic pulmonary arterial hypertension (IPAH) is a fatal disease characterised by elevated blood pressure in the pulmonary circulation. Initial vasoconstriction, proliferation of pulmonary arterial smooth muscle cells (PASMC) and increased deposition of extracellular matrix (ECM) contribute to pathological remodelling of pulmonary arterioles in IPAH. Glycosaminoglycans (GAGs), components of the ECM, control cellular proliferation and differentiation, but their expression in IPAH remains elusive.**

**In the present study, GAG expression was investigated in the lungs of patients with IPAH or control transplant donors, and expression and localisation of GAG-metabolising enzymes were analysed *in vivo* and *in vitro*.**

**A significant increase in the expression of hyaluronic acid (HA) was detected in IPAH lungs, associated with increased hyaluronan synthase (*Has*)*1* and decreased hyaluronoglucosaminidase 1 gene expression, as assessed by quantitative RT-PCR and Western blotting. HAS1 protein localised to PASMC *in vivo* and increased HA deposition was observed in remodelled pulmonary arteries in IPAH. Transforming growth factor-β1, a profibrotic growth factor, led to increased HA secretion and HAS1 expression in primary PASMC.**

**The results demonstrate an increased hyaluronic acid content in idiopathic pulmonary arterial hypertension lungs, associated with increased hyaluronan synthase 1 and decreased hyaluronoglucosaminidase 1 gene expression. Synergistic regulation of glycosaminoglycan-metabolising enzymes in favour of accumulation may, thus, regulate pathological vascular remodelling in idiopathic pulmonary arterial hypertension lungs.**

**KEYWORDS: Hyaluronic acid, pulmonary arterial hypertension, pulmonary arterial smooth muscle cells, transforming growth factor-β1, vascular remodelling**

Idiopathic pulmonary arterial hypertension (IPAH) is a rare but fatal disease characterised by elevated blood pressure in the pulmonary circulation due to increased vascular resistance of pulmonary arterioles [1, 2]. If untreated, IPAH leads to right ventricular hypertrophy and failure and subsequent death. Early in disease pathogenesis, endothelial cell dysfunction triggers increased vasoconstriction and *in situ* thrombosis. This is followed by pathological vascular remodelling, a process characterised by intimal fibrosis and thickening of the medial and adventitial layers due to uncontrolled proliferation of pulmonary arterial smooth muscle cells (PASMC) and perivascular fibroblasts [3–5]. In parallel, enhanced cellular activation of PASMC and fibroblasts leads to excessive extracellular matrix (ECM) deposition, which potentiates the increased stiffness of pulmonary arteries in IPAH [6, 7].

Altered ECM turnover is a hallmark of several pulmonary diseases, including adult respiratory distress syndrome, asthma, idiopathic pulmonary fibrosis, or chronic obstructive lung disease, which underlines the importance of ECM homeostasis for proper lung function [7–9]. In the lung, the ECM is subjected to a daily turnover of ~10% of total ECM, indicating that subtle changes in turnover rates accumulate to produce large changes in total ECM composition with time [10]. The ECM is largely composed of collagens, fibronectin, vitronectin, proteoglycans and glycosaminoglycans (GAGs) [11]. GAGs are linear acidic polysaccharides of variable length and composition that are grouped into four major categories: hyaluronic acid (HA); heparin and heparan sulphate (HS); chondroitin and dermatan sulphates (CS and DS, respectively); and keratan sulphate [12, 13]. GAGs have previously been shown to control lung inflammation, as well as the phenotype of systemic vascular smooth muscle cells [14–16].

HA is a major component of the basement membrane and constitutes ~10% of all proteoglycans [17].

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# The effect of OSAS on sick leave and work disability

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**ABSTRACT: The objective of the present study was to examine the independent contribution of symptoms of obstructive sleep apnoea syndrome (OSAS) to long-term sick leave and permanent work disability.**

**Using a historical cohort design with 4 yrs of follow-up, information on sick leave and disability benefit recipiency were merged with health information from the Hordaland Health Study, carried out in western Norway during 1997–1999. Persons aged 40–45 yrs (n=7,028) were assessed for self-reported symptoms of OSAS (snoring, breathing cessations and daytime sleepiness), body mass index, somatic conditions and other potential confounders. The outcomes, cumulative sick leave of ⩾8 weeks and permanent work disability, were identified in records from the National Insurance Administration.**

**After excluding participants with work disability at baseline, symptoms of OSAS were found to be a significant predictor of both subsequent long-term sick leave and permanent work disability. These effects remained significant after adjustment for a range of possible confounding factors. Daytime sleepiness showed the greatest explanatory power, followed by breathing cessations and snoring.**

**It is concluded that self-reported symptoms of obstructive sleep apnoea syndrome are an independent risk factor for subsequent long-term sick leave and permanent work disability. These findings need to be replicated using objective measures of obstructive sleep apnoea syndrome.**

**KEYWORDS: Epidemiology, obstructive, population-based, risk factors, sickness absence, sleep apnoea**

Obstructive sleep apnoea syndrome (OSAS) is a sleep disorder in which the upper airway closes repeatedly during sleep, leading to sleep fragmentation and decreased levels of oxyhaemoglobin saturation [1]. The prevalence of OSAS is estimated to be ~5% [2–8], but the at-risk population is likely to be much larger [9]; only 10% of the population are adequately screened for this diagnosis [10]. Clinically characterised by snoring, breathing cessations and extreme daytime somnolence [11], OSAS has been shown to be a risk factor for a range of medical conditions, including glucose intolerance [12], impotence [13], hypertension [14], myocardial infarction [15], and stroke and mortality [16]. Untreated OSAS also increases the risk of automobile accidents [17], leads to poor quality of life [18] and has been linked with several neurocognitive consequences [19, 20].

In addition to such impacts on individual health, an Australian study recently estimated the economic costs of sleep disorders (OSAS and insomnia being the most important) to represent almost 1% of Australia's gross domestic product [21]. In addition, despite previous studies consistently showing self-reported sleep problems in general to be a significant risk factor for both long-term sick leave and permanent work disability determined objectively [22–24], the only recent study investigating OSAS severity and self-reported work limitation yielded mixed results [25]. To the best of the present authors' knowledge, no studies to date have prospectively aimed to study the independent effects of symptoms of OSAS on long-term sick leave or permanent work disability.

Although polysomnography (PSG) is recommended for making the diagnosis of OSAS, it is not easily applied in large population-based studies, being intrusive, impractical and expensive. Therefore, screening instruments based on self-reported symptoms of OSAS have been necessary in order to gain information on both

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# CPAP and measures of cardiovascular risk in males with OSAS

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**ABSTRACT: Obstructive sleep apnoea syndrome (OSAS) has been associated with hypertension, stroke and myocardial ischaemia in epidemiological and observational studies. Continuous positive airway pressure (CPAP) is the treatment of choice for OSAS, but the impact of this intervention on established risk factors for cardiovascular disease remains incompletely understood.**

**A total of 102 males with moderate-to-severe OSAS were randomised to therapeutic (n=51) or subtherapeutic (n=51) CPAP treatment for 4 weeks to investigate the effects of active treatment on 24-h urinary catecholamine excretion, baroreflex sensitivity (BRS), arterial stiffness (augmentation index) and 24-h ambulatory blood pressure (ABP).**

**After 4 weeks of therapeutic CPAP, significant reductions were seen in urine normetanephrine excretion (from mean±SD 179.7±80.1 to 132.7±46.5 μmol·mol$^{-1}$ creatinine) and augmentation index (from 14.5±11.3 to 9.1±13.8%) compared with the subtherapeutic control group. Furthermore, therapeutic CPAP significantly improved BRS (from 7.1±3.3 to 8.8±4.2 ms·mmHg$^{-1}$) and reduced mean arterial ABP by 2.6±5.4 mmHg.**

**In conclusion, treatment of obstructive sleep apnoea with continuous positive airway pressure may lower cardiovascular risk by reducing sympathetic nerve activity, ambulatory blood pressure and arterial stiffness and by increasing sensitivity of the arterial baroreflex.**

**KEYWORDS: Arterial stiffness, baroreflex, catecholamines, continuous positive airway pressure, obstructive sleep apnoea**

Obstructive sleep apnoea syndrome (OSAS) is characterised by repetitive apnoea/hypopnoea during sleep associated with oxygen desaturations and sleep disruption. It has been estimated that 2–4% of the adult population in Western countries suffer from clinically significant OSAS, and it is becoming more prevalent as the average bodyweight of the population rises [1].

OSAS has been associated with hypertension, stroke and myocardial ischaemia in epidemiological and prospective observational studies [1, 2]. The pathophysiological mechanisms underlying the association between OSAS and cardiovascular disease are not fully understood, and indeed there may not be a causal relationship. During the actual repetitive episodes of apnoeas there is increased inspiratory effort, episodic hypoxaemia, recurrent arousals, reflex sympathetic activation, increased arterial stiffness and consequent marked transient increases in arterial blood pressure [3–5]. The prolonged repetitive rises in blood pressure are likely to induce excessive vascular shear stress, which has been shown to contribute to the formation of atherosclerotic plaques [6].

Sympathetic activity has been shown to be increased even in the daytime in patients with OSAS, both from measurements of circulating catecholamines and sympathetic nerve traffic. Augmented sympathetic activation may increase arterial stiffness and blunt baroreflex sensitivity (BRS), both of which may contribute to the development of arterial hypertension and to increased mortality [7–12].

Continuous positive airway pressure (CPAP) is the treatment of choice for patients with symptomatic OSAS, as it has been shown to improve daytime sleepiness, alertness and quality of life and to decrease blood pressure [13–15]. Whether CPAP treatment is effective in counteracting the autonomic imbalance and increased arterial stiffness in patients with OSAS remains a matter of debate.

The current authors have addressed this uncertainty by examining changes in 24-h urinary catecholamine excretion, BRS, arterial stiffness

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# Sleep-disordered breathing in unilateral diaphragm paralysis or severe weakness

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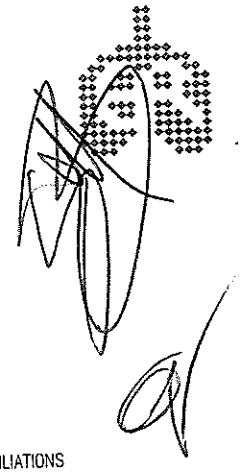

ABSTRACT: Few data exist concerning sleep in patients with hemidiaphragm paralysis or weakness. Traditionally, such patients are considered to sustain normal ventilation in sleep.

In the present study, diaphragm strength was measured in order to identify patients with unilateral paralysis or severe weakness. Patients underwent polysomnography with additional recordings of the transoesophageal electromyogram (EMG) of the diaphragm and surface EMG of extra-diaphragmatic respiratory muscles. These data were compared with 11 normal, healthy subjects matched for sex, age and body mass index (BMI).

In total, 11 patients (six males, mean±SD age 56.5±10.0 yrs, BMI 28.7±2.8 kg·m$^{-2}$) with hemidiaphragm paralysis or severe weakness (unilateral twitch transdiaphragmatic pressure 3.3±1.7 cm$H_2O$ (0.33±0.17 kPa) were studied. They had a mean±SD respiratory disturbance index of 8.1±10.1 events·h$^{-1}$ during non-rapid eye movement (NREM) sleep and 26.0±17.8 events·h$^{-1}$ during rapid eye movement (REM) sleep (control groups 0.4±0.4 and 0.7±0.9 events·h$^{-1}$, respectively). The diaphragm EMG, as a percentage of maximum, was double that of the control group in NREM sleep (15.3±5.3 *versus* 8.9±4.9% max, respectively) and increased in REM sleep (20.0±6.9% max), while normal subjects sustained the same level of activation (6.2±3.1% max).

Patients with unilateral diaphragm dysfunction are at risk of developing sleep-disordered breathing during rapid eye movement sleep. The diaphragm electromyogram, reflecting neural respiratory drive, is doubled in patients compared with normal subjects, and increases further in rapid eye movement sleep.

KEYWORDS: Electromyogram, rapid eye movement sleep, respiratory muscles

Patients with diaphragm paralysis may develop breathlessness as a consequence of the reduced capacity of the respiratory system [1, 2]. During sleep in normal subjects, ventilation depends particularly on diaphragm function [3]. In patients with diaphragm dysfunction, during both rapid eye movement (REM) sleep and wakefulness, electromyographic activity of the extradiaphragmatic respiratory muscles [4–7] is higher than normal as a compensation for diaphragm weakness.

The results of studies looking at breathing patterns in unilateral or bilateral diaphragm paralysis (UDP and BDP, respectively) have been inconsistent [8–13]. Some studies have reported disturbed sleep, inadequate ventilation during sleep and daytime sleepiness caused by diaphragm dysfunction [8, 11], while others have found little impact on the normal sleep pattern unless there is additional load on the ventilatory system [9, 10, 14]. Previous studies either did not focus on UDP (had mixed populations of BDP and UDP [8, 9] or exclusively BDP [5, 11] patients), did not distinguish between REM and non-REM (NREM) sleep-associated sleep-disordered breathing (SDB) [10], did not characterise the subjects other than with noninvasive measurements [15] or studied animal models. Therefore, the studies that did not perform invasive respiratory muscle tests did not test a homogenous population of UDP patients and it is likely that the different results reflect the heterogeneity of the patients studied, in terms of weakness and ventilatory load.

Clinically it is often assumed that patients with UDP have no problems during sleep unless other comorbidities are present [9, 10]. It has previously been noted that some patients with

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PERSPECTIVE

# The Brussels Declaration: the need for change in asthma management

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**ABSTRACT: Asthma is a highly prevalent condition across Europe and numerous guidelines have been developed to optimise management. However, asthma can be neither cured nor prevented, treatment choices are limited and many patients have poorly controlled or uncontrolled asthma.**

**The Brussels Declaration on Asthma, sponsored by The Asthma, Allergy and Inflammation Research Charity, was developed to call attention to the shortfalls in asthma management and to urge European policy makers to recognise that asthma is a public health problem that should be a political priority.**

**The Declaration urges recognition and action on the following points: the systemic inflammatory component of asthma should be better understood and considered in assessments of treatment efficacy; current research must be communicated and responded to quickly; the European Medicines Agency guidance note on asthma should be updated; "real world" studies should be funded and results used to inform guidelines; variations in care across Europe should be addressed; people with asthma should participate in their own care; the impact of environmental factors should be understood; and targets should be set for improvement.**

**The present paper reviews the evidence supporting the need for change in asthma management and summarises the ten key points contained in the Brussels Declaration.**

KEYWORDS: **Asthma, management, the Brussels Declaration**

The prevalence of asthma has increased dramatically over the last 20 yrs [1] and ~180,000 deaths annually are attributable to asthma worldwide. The disease has become particularly common in industrialised countries, where it has become the most common chronic disease among children [2]. As a result of the high prevalence and ongoing changes to treatment guidelines, it has been difficult to make an accurate estimate of the current cost of asthma. In Europe, the annual cost was estimated at €17.7 billion in 2003 (€9.8 billion in lost productivity and €7.9 billion in direct medical costs) [3].

The increase in asthma prevalence over recent decades has been accompanied by an increase in atopic sensitisation and allergic conditions such as rhinitis and sinusitis, suggesting that there may be a systemic component to the inflammation associated with asthma [4–6]. Despite the increasing evidence of the systemic inflammation model and the emerging data suggesting a role for inflammation in structural remodelling of the airways [7, 8], many patients remain reliant on medications that relieve symptoms or treat inflammation only within the lower airways [9, 10]. The root causes of the inflammation associated with asthma have not been clarified and consequently its development cannot be prevented.

Although a great deal of work has been done to improve the understanding of asthma, knowledge in many areas remains suboptimal. Diagnosis can be difficult due to the number of different diseases with similar presentations and because there is no single measure or instrument that can provide definitive proof that asthma is present [11]. Once the diagnosis is in place, many patients are inadequately informed and educated about the treatment goals and many fail to achieve asthma control [12, 13]. In addition, currently available asthma medications that can help patients achieve control are being used suboptimally. Children represent a particular problem because few clinical trials address the efficacy and safety of asthma treatment in paediatric patients and the disease course in

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# Circulating fibronectin to C-reactive protein ratio and mortality: a biomarker in COPD?

**S.F.P. Man, L. Xing, J.E. Connett, N.R. Anthonisen, R.A. Wise, D.P. Tashkin, X. Zhang, R. Vessey, T.G. Walker, B.R. Celli and D.D. Sin**

ABSTRACT: **The balance between inflammatory and repair processes is important in maintaining lung homeostasis in chronic obstructive pulmonary disease (COPD). The aim of the present study was to determine whether or not an integrated index of a biomarker involved in inflammation, C-reactive protein (CRP), and another involved in wound repair, fibronectin, may be a good measure to predict clinical outcomes in COPD.**

**Circulating blood levels of CRP and fibronectin were measured in 4,787 individuals with mild-to-moderate COPD who were prospectively followed for >7 yrs after blood collection as part of the Lung Health Study. To assess the balance between repair and inflammation, a simple ratio was calculated by dividing fibronectin levels by CRP levels and a Cox proportional hazards model was used to determine the relationship between this ratio and all-cause and disease-specific causes of mortality.**

**The relationship between the fibronectin to CRP ratio and all-cause mortality was L-shaped. There was an exponential decay in the adjusted hazard function (*i.e.* the risk of mortality) as the ratio decreased until a value of 148 was reached, beyond which point the hazard function did not change significantly. Similar results were observed for the risk of coronary and cardiovascular mortality.**

**Circulating fibronectin to CRP ratio is significantly associated with all-cause mortality of COPD patients. However, in contrast to other biomarkers, the relationship appears to be L-shaped (and not linear), suggesting a threshold at ~150. While promising, future studies are needed to validate this simple index as a biomarker in COPD.**

KEYWORDS: **Chronic obstructive pulmonary disease, C-reactive protein, fibronectin, inflammation, mortality, repair**

Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease in the western world, affecting 10–15% of the adult population over the age of 45 yrs [1]. Within 15 yrs, COPD will be the third leading cause of mortality and the fifth leading cause of disability worldwide [2]. Unfortunately, there is a dearth of effective therapies that can prolong survival of COPD patients [3]. The development of novel therapeutic compounds for COPD has been impeded by a scarcity of robust intermediate end-points that can track disease progression and predict morbidity and mortality [4]. The pressing need for effective intermediate end-points for COPD therapeutic trials was highlighted by the American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force statement on outcomes for COPD pharmacological trials [5]. With the growing awareness of COPD as a systemic disease, there has been a shift in the emphasis of biomarker discovery towards blood specimens [6]. Serum or plasma biomarkers are attractive because blood, unlike bronchial washes or brushes, is readily available and the measurements can be easily standardised. To date, most of the attention has been focused on biomarkers associated with the systemic inflammatory pathway and some of these markers show promise, most notably C-reactive protein (CRP) [7–9]. Another important but less studied pathway is wound repair [10]. Over- or underexpression of the reparative pathway can lead to disease states [11]. One possible blood biomarker of the reparative system is fibronection. Fibronectin is a high

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# Role of 2-month sputum smears in predicting culture conversion in pulmonary tuberculosis

**W-J. Su*,#, J-Y. Feng*,#, Y-C. Chiu*, S-F. Huang* and Y-C. Lee*,#**

**ABSTRACT: Sputum smears and culture conversion are frequently used to evaluate treatment response in pulmonary tuberculosis patients. Limited data are available on the evaluation of the correlation between under-treatment sputum smear results and culture conversion.**

**This prospective study included sputum culture-proven pulmonary tuberculosis patients at six hospitals in Taiwan. At least two sets of sputum were collected at the completion of 8 weeks of TB treatment. The sensitivities and specificities of 2-month sputum smears were estimated based on culture conversion status.**

**A total of 371 patients were enrolled for analysis. Factors associated with culture conversion included having a smear positive before treatment, presence of a cavity on radiography, rifampicin resistance and usage of the DOTS (directly observed therapy, short course) strategy. The sensitivities of 2-month sputum smears for culture conversion among all patients, initially smear-positive patients and initially smear-negative patients were 64.3, 71.4 and 38%, respectively, and the specificities were 81.6, 69.9 and 92.8%, respectively. In patients who were 2-month sputum smear-positive, the 2-month culture conversion rate was 80% if the patients were under DOTS and without cavitary lesions in radiograms.**

**The predictive value of 2-month sputum smears in culture conversion was limited and highly influenced by clinical factors in pulmonary tuberculosis patients.**

**KEYWORDS: Culture, directly observed therapy short course implementation, *Mycobacterium tuberculosis*, pulmonary tuberculosis, sputum**

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Pulmonary tuberculosis (PTB) is an airborne infectious disease that requires multiple-drug combination therapy and long treatment duration. Despite great advances in molecular diagnosis, sputum cultures of *Mycobacterium tuberculosis* (MTB) remain the gold standard for PTB diagnosis. After initiation of anti-tuberculosis (anti-TB) treatment, sputum acid-fast bacilli (AFB) smears and cultures of MTB are regularly checked during the treatment period and serve as important indicators of treatment response.

Achievement of sputum sterilisation, which is determined by sputum culture conversion, is a cardinal index of treatment success. Previous studies have demonstrated that the time to sputum negativity is an important determinant of relapse [1–3]. Failure to achieve sputum culture conversion in <2 months will lead to a worse treatment outcome [4]. Documentation of sputum culture conversion is also recommended as a necessary criterion before completion of anti-TB treatment in current treatment guidelines [5]. Based on the high predictive value of sputum culture conversion in treatment response [4, 6, 7], identification of the clinical factors that are associated with a lower sputum culture conversion rate is of crucial importance in PTB management [8–10].

In spite of the high accuracy of sputum culture conversion in the assessment of treatment response, the long yield time limits its usefulness in clinical practice. As a simple and rapid test, sputum smears are frequently adopted as a substitute for sputum cultures to evaluate infectivity and treatment effectiveness. However, positive sputum AFB smears with negative results for MTB culture are not unusual during the course of anti-TB treatment. A false-positive sputum AFB smear (AFB smear positive but MTB culture negative) may lead to the physician making the wrong judgement and thereby wasting medical resources unnecessarily. Therefore, the predictive value of sputum AFB smears in

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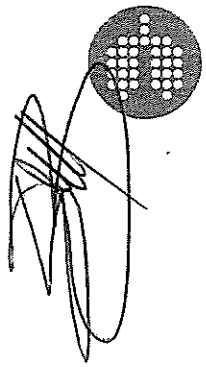

# Factors associated with inflammatory cytokine patterns in community-acquired pneumonia

**R. Martínez*,#, R. Menéndez*,#, S. Reyes*, E. Polverino', C. Cillóniz', A. Martínez*, C. Esquinas', X. Filella+, P. Ramírez#,§ and A. Torres#,',j**

**ABSTRACT: Raised systemic levels of interleukin (IL)-6 and IL-10 cytokines have been associated with poorer outcome in community-acquired pneumonia. The aim of our study was to identify potential associated factors with increased levels of IL-6, IL-10, or both cytokines.**

**We performed a prospective study of 685 patients admitted to hospital with community-acquired pneumonia. IL-6 and IL-10 were measured in blood in the first 24 h.**

**30-day mortality increased from 4.8% to 11.4% (p=0.003) when both cytokines were higher than the median. Independent associated factors with an excess of IL-6 were neurologic disease, confusion, serum sodium <130 mEq·L$^{-1}$, pleural effusion, and bacteraemia. The associated factors for an excess of IL-10 were respiratory rate ⩾30 breaths·min$^{-1}$, systolic blood pressure <90 mmHg and glycaemia ⩾250 mg·dL$^{-1}$. The independent associated factors for an excess of both cytokines were confusion, systolic blood pressure <90 mmHg, pleural effusion and bacteraemia. Protective factors were prior antibiotic treatment and pneumococcal vaccination.**

**Different independent factors are related to an excess of IL-6 and IL-10. Confusion, hypotension, pleural effusion and bacteraemia were associated with the inflammatory profile with the highest mortality rate, whereas anti-pneumococcal vaccination and previous antibiotic treatment appeared to be protective factors.**

**KEYWORDS: Associated factors, cytokine excess in community-acquired pneumonia, interleukin-6, interleukin-10, mortality**

Community-acquired pneumonia (CAP) remains the most frequent cause of death due to infection in developed countries [1], despite advances in antimicrobial therapy and improved management of this disease. The estimated incidence of community-acquired pneumonia is between 3 and 5 cases per 1,000 inhabitants per year, and it is more frequent early and late in life [2]. About one-third of patients with CAP will require hospitalisation.

An inflammatory response of the host to the causal microorganisms occurs in CAP, with the release of pro- and anti-inflammatory cytokines. Although this cytokine production is necessary for the defence function, an excessive response can cause a deleterious effect. In recent years, there has been increased interest concerning the inflammatory response to infections and its relation to outcome. An excess of pro-inflammatory cytokines [3, 4] has proven to be a strong predictor of treatment failure and mortality in CAP and sepsis. In a study performed in hospitalised patients with CAP [5], we found that initial increases in interleukin (IL)-6 and/or IL-8 and their persistence 72 h after treatment correlated with antibiotic treatment failure. KELLUM *et al.* [6], in a large study in CAP patients with or without sepsis, found that mortality in CAP is higher when both levels of IL-6 (pro-inflammatory) and IL-10 (anti-inflammatory) cytokines are raised. This article illustrates the heterogeneity in the inflammatory response in CAP, with different activation patterns of cytokines; this may reflect the implication of different factors in the synthesis of each cytokine.

Our hypothesis is that the excess of systemic levels of cytokines like IL-6 and IL-10 is associated with different factors, whose identification may contribute to a better understanding of the host response to infection. The aim of our study was to measure the systemic cytokine response to infection in hospitalised CAP patients in order to evaluate different inflammatory profiles or patterns (increase in IL-6, IL-10 or both), and to

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# Steroids induce a disequilibrium of secreted interleukin-1 receptor antagonist and interleukin-1β synthesis by human neutrophils

**J.D. Langereis, E-J.D. Oudijk, R.C. Schweizer, J-W.J. Lammers, L. Koenderman and L.H. Ulfman**

ABSTRACT: **Chronic obstructive pulmonary disease (COPD) is characterised by neutrophilic inflammation in the airways and these neutrophils contribute to the production of inflammatory mediators. Dampening the production of proinflammatory mediators might be an important strategy to treat COPD and glucocorticosteroids are known to do so *via* inhibition of nuclear factor-κB. However, this pathway is important for the control of pro- and anti-inflammatory genes.**

**We studied the effects of dexamethasone on production and secretion of pro-inflammatory interleukin (IL)-1β and anti-inflammatory secreted IL-1 receptor antagonist (sIL-1Ra) by human neutrophils activated with tumor necrosis factor (TNF)-α.**

***In vitro*, TNF-α-stimulated neutrophils produced significant amounts of IL-1β and sIL-1Ra; this production was inhibited by dexamethasone. However, synthesis and secretion of sIL-1Ra was inhibited at lower concentrations dexamethasone compared to IL-1β, which changed the IL-1β:sIL-1Ra ratio significantly. This altered ratio resulted in a more pro-inflammatory condition, as visualised by increased intercellular adhesion molecule-1 expression on human endothelial cells. *In vivo*, moderate-to-severe COPD patients using inhaled glucocorticosteroids have decreased plasma sIL-Ra levels compared with mild-to-moderate patients not on glucocorticosteroid treatment.**

**In conclusion, dexamethasone induces a pro-inflammatory shift in the IL-1β:sIL-1Ra cytokine balance in neutrophils *in vitro*, which might contribute to a lack of endogenous anti-inflammatory signals to dampen inflammation *in vivo*.**

KEYWORDS: **Chronic obstructive pulmonary disease, glucocorticosteroids, interleukin-1β, interleukin-1 receptor antagonist, neutrophil**

The incidence of chronic obstructive pulmonary disease (COPD) is increasing and has been predicted to become the third most common cause of death in the world by 2020 [1]. COPD is an inflammatory disease of the lungs and treatment of stable COPD patients with conventional anti-inflammatory treatment, such as inhaled glucocorticosteroids (GCS), is ineffective [2]. The chronic inflammatory response found in the lungs is characterised predominantly by an accumulation of neutrophils, but macrophages, B-cells and CD8+ T-cells are also involved [3]. Furthermore, increased neutrophil numbers are found in bronchial alveolar lavage (BAL) fluid, induced sputum [4] and bronchial biopsy specimens [5]. These neutrophils synthesise cytokines, chemokines and other inflammatory mediators that are known to contribute to the inflammation in the lungs and other organs [6–8]. Limited data on the effects of inhaled GCS on these extrapulmonary effects of COPD are available [9, 10].

Glucocorticosteroids elicit their function through binding to the glucocorticoid receptor (GR). Two main variants of GR, GRα and GRβ, are expressed in various inflammatory cells and tissues, including neutrophils [11]. GRα is a ligand-dependent transcription factor, which binds glucocorticoid response elements (GRE) in DNA and, subsequently, regulates GR target genes [12]. GRα has also been shown to interact with other transcription factors, such as activator protein (AP)-1 [13] and nuclear factor (NF)-κB [14, 15], and, thereby, modulate gene transcription. In contrast, GRβ does not activate GR-responsive genes [16],

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# Whole-body resting and exercise-induced lipolysis in sarcopaenic patients with COPD

**F.M.E. Franssen*, H.P. Sauerwein#, E.P.A. Rutten*, E.F.M. Wouters* and A.M.W.J. Schols***

ABSTRACT: Impaired β-adrenoceptor-mediated lipolysis has been reported in sarcopaenic chronic obstructive pulmonary disease (COPD) patients. This could play a role in the shift in body composition towards decreased fat-free mass (FFM) and relative maintenance of fat mass (FM). Lipolysis could be affected by chronic treatment with $\beta_2$-agonists or disease-related factors. Therefore, whole-body resting and exercise-induced lipolysis were investigated in sarcopaenic COPD patients with moderate disease severity.

Seven sarcopaenic COPD patients (mean±SEM forced expiratory volume in one second ($FEV_1$) 53±5% of the predicted value; body mass index (BMI) 27.5±0.9 $kg \cdot m^{-2}$) and seven controls matched for age, sex and BMI were studied. In addition, six underweight COPD patients ($FEV_1$ 51±5% pred; BMI 20.6±0.7 $kg \cdot m^{-2}$) matched for disease severity were recruited. Lipolysis and plasma levels of catecholamines were assessed during infusion of [$^2H_5$]glycerol at rest and during submaximal cycling exercise.

The proportional FM was comparable between sarcopaenic patients and controls, whereas the FFM index was significantly reduced in patients. At rest, the rate of appearance ($R_a$) of glycerol (4.1±0.6 and 3.3±0.2 $\mu mol \cdot kg\ FFM^{-1} \cdot min^{-1}$, respectively) did not differ significantly. In underweight patients, glycerol $R_a$ (4.3±0.5 $\mu mol \cdot kg\ FFM^{-1} \cdot min^{-1}$) was also comparable. End-of-exercise lipolytic rates did not differ significantly between groups. Glycerol $R_a$ was not related to FM. Resting adrenalin levels were significantly increased in underweight COPD patients and were related to resting lipolysis.

Sarcopaenia in chronic obstructive pulmonary disease patients with moderate disease severity is not characterised by an abnormal lipolytic rate. Altered regulation of muscle protein turnover seems to be the trigger in the body compositional shift observed in these patients.

KEYWORDS: Body composition, chronic obstructive pulmonary disease, exercise, fat mass, intermediary metabolism, lipolysis

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Cachexia, defined as weight loss with a disproportional loss of fat-free mass (FFM), occurs in a substantial number of patients with chronic obstructive pulmonary disease (COPD) and is an independent predictor of mortality [1]. Its prevalence depends upon the population analysed, and ranges from 11% in moderate-to-severe COPD outpatients [2] to 26% in severe patients eligible for pulmonary rehabilitation [3]. Furthermore, in a substantial proportion (10–15%) of normal-weight COPD patients, hidden depletion of FFM occurs [3, 4], also referred to as sarcopaenia. The clinical implications of this body compositional shift towards decreased FFM and relative or even absolute abundance of fat mass (FM) were illustrated in a study showing a greater degree of physical impairment in normal-weight COPD patients with low FFM compared to underweight patients with preserved FFM [3]. It was hypothesised that sarcopaenia in COPD is associated with alterations in intermediary metabolism, towards accelerated net muscle protein breakdown and impaired fat oxidation or decreased lipolysis. There are some indications that depletion of FFM is indeed associated with altered regulation of protein turnover towards increased protein breakdown [5–7]. In addition, reduced skeletal muscle activity of 3-hydroxyacyl CoA dehydrogenase, which regulates the β-oxidation of fatty acids, has consistently been shown in normal-weight COPD patients [8]. Finally, an impaired β-adrenoceptor-mediated increase in plasma levels of nonesterified fatty acids was reported in sarcopaenic COPD patients [9], which is suggestive of reduced lipolysis. However, whole-body

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REVIEW

# Impact of inspiratory muscle training in patients with COPD: what is the evidence?

R. Gosselink*,#, J. De Vos*,#, S.P. van den Heuvel*, J. Segers*,#, M. Decramer*,# and G. Kwakkel+

ABSTRACT: A meta-analysis including 32 randomised controlled trials on the effects of inspiratory muscle training (IMT) in chronic obstructive pulmonary disease (COPD) patients was performed. Overall and subgroup analyses with respect to training modality (strength or endurance training, added to general exercise training) and patient characteristics were performed. Significant improvements were found in maximal inspiratory muscle strength ($P_{I,max}$; +13 $cmH_2O$), endurance time (+261 s), 6- or 12-min walking distance (+32 and +85 m respectively) and quality of life (+3.8 units). Dyspnoea was significantly reduced (Borg score -0.9 point; Transitional Dyspnoea Index +2.8 units). Endurance exercise capacity tended to improve, while no effects on maximal exercise capacity were found. Respiratory muscle endurance training revealed no significant effect on $P_{I,max}$, functional exercise capacity and dyspnoea. IMT added to a general exercise programme improved $P_{I,max}$ significantly, while functional exercise capacity tended to increase in patients with inspiratory muscle weakness ($P_{I,max}$ <60 $cmH_2O$).

IMT improves inspiratory muscle strength and endurance, functional exercise capacity, dyspnoea and quality of life. Inspiratory muscle endurance training was shown to be less effective than respiratory muscle strength training. In patients with inspiratory muscle weakness, the addition of IMT to a general exercise training program improved $P_{I,max}$ and tended to improve exercise performance.

KEYWORDS: Meta-analysis, muscle training, respiratory muscles, systematic review

Respiratory muscle weakness is observed in chronic obstructive pulmonary disease (COPD) patients [1, 2] and contributes to hypercapnia [3], dyspnoea [4, 5], nocturnal oxygen desaturation [6] and reduced walking distance [7]. During exercise it has been shown that diaphragm work is increased in COPD [8] and COPD patients use a larger proportion of the maximal inspiratory pressure ($P_{I,max}$) than healthy subjects [9]. This pattern of breathing is closely related to the dyspnoea sensation during exercise [9] and might potentially induce respiratory muscle fatigue. However, diaphragmatic fatigue was not demonstrated after exhaustive exercise [10]. Studies in patients with COPD have shown natural adaptations of the diaphragm to greater oxidative capacity and resistance to fatigue [11–13]. The abovementioned considerations gave conflicting arguments to the rationale of respiratory muscle training in COPD. Current guidelines [14, 15] and meta-analyses [16–20] are not undisputedly positive on the application of inspiratory muscle training (IMT). From meta-analyses it is clear that IMT increases inspiratory muscle strength and endurance, and decreases dyspnoea. However, exercise performance and quality of life did not improve significantly [18, 20, 21]. The addition of IMT to a general exercise programme did not improve exercise performance [20]. Furthermore, differences in effects of resistance and endurance training were never analysed, while patient characteristics relevant for favourable effects of IMT have not been identified so far. Finally, many randomised controlled trials have been published since our previous meta-analysis, offering more input for more extensive analysis. The aim of the

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# Usefulness of serum procalcitonin levels in pulmonary tuberculosis

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ABSTRACT: **There are very few data on serum procalcitonin (PCT) levels in pulmonary tuberculosis (PTB) patients who are negative for HIV.**

**We assessed serum PCT in consecutive patients diagnosed with pulmonary tuberculosis or community-acquired pneumonia (CAP) on admission to discriminate between PTB and CAP, and examined the value of prognostic factors in PTB.**

**102 PTB patients, 62 CAP patients, and 34 healthy volunteers were enrolled. Serum PCT in PTB patients was significantly lower than in CAP patients (mean±SD 0.21±0.49 *versus* 4.10±8.68 ng·mL$^{-1}$; p<0.0001). By receiver-operating characteristic curve analysis, serum PCT was an appropriate discrimination marker for PTB and CAP (area under the curve 0.866). PTB patients with ⩾0.5 ng·mL$^{-1}$ (normal cut-off) had significantly shorter survival than those with <0.5 ng·mL$^{-1}$ (p<0.0001).**

**Serum PCT is not habitually elevated in HIV-negative PTB patients and is a useful biomarker for discriminating between PTB and CAP; however, when serum PCT is outside the normal range, it is a poor prognostic marker.**

KEYWORDS: **Procalcitonin, prognosis, pulmonary tuberculosis**

Procalcitonin (PCT), the precursor molecule of calcitonin, is known as a systemic inflammatory protein. Several studies have reported that serum PCT is a useful biomarker for diagnosis and for estimating the severity of community-acquired pneumonia (CAP) [1, 2]. In particular, high serum PCT with CAP is associated with a high mortality rate [3–7]. In contrast to CAP, there are very few data on PCT levels in pulmonary tuberculosis (PTB). According to the limited information available from small scale studies, which included 27 PTB patients [8], 30 PTB patients [9], and 34 HIV-positive PTB patients [10], serum PCT was not elevated; however, the clinical significance of serum PCT levels in PTB patients has not been well documented. In this study, we examined serum PCT levels in HIV-negative PTB patients to discriminate between PTB and CAP. Moreover, we investigated whether serum PCT levels in PTB patients are related to disease prognosis.

## METHODS

### *Patients*

From June 2008 to September 2009, consecutive patients admitted to our hospital (Tenryu Hospital, Hamamatsu, Japan) with PTB or CAP were included in this study. PTB was defined by sputum smear-positive and culture-positive *Mycobacterium tuberculosis* in the presence of new radiographic pulmonary infiltration. According to the European consensus on the surveillance of tuberculosis [11], PTB patients with tuberculous involvement of other organ systems were defined as having disseminated tuberculosis. Patients with other infections, such as urinary tract infection, meningitis and infectious endocarditis, were excluded. All PTB patients were initially treated with a standard four-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin.

Pneumonia was diagnosed by the presence of new radiographic pulmonary infiltration and the following clinical findings: 1) axillary temperature >37.5°C; and 2) a cough, purulent sputum, pleuritic chest pain or shortness of breath. CAP was defined if pneumonia had occurred at home without antibiotic use in the previous 14 days.

As the severity index, the Pneumonia Patients Outcome Research Team score [12] was used in all PTB and CAP patients. Healthy volunteers free from respiratory disease were included as normal controls.

This study was prospective and was approved by the ethics committee of our hospital, and informed consent was obtained according to the hospital's guidelines.

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# Procedure volume is one determinant of centre effect in mechanically ventilated patients

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ABSTRACT: **Survival rates vary significantly between intensive care units, most notably in patients requiring mechanical ventilation (MV). The present study sought to estimate the effect of hospital MV volume on hospital mortality.**

**We included 179,197 consecutive patients who received mechanical ventilation in 294 hospitals. Multivariate logistic regression models with random intercepts were used to estimate the effect of annual MV volume in each hospital, adjusting for differences in severity of illness and case mix.**

**Median annual MV volume was 162 patients (interquartile range 99–282). Hospital mortality in MV patients was 31.4% overall, 40.8% in the lowest annual volume quartile and 28.2% in the highest quartile. After adjustment for severity of illness, age, diagnosis and organ failure, higher MV volume was associated with significantly lower hospital mortality among MV patients (OR 0.9985 per 10 additional patients, 95% CI 0.9978–0.9992; p=0.0001). A significant centre effect on hospital mortality persisted after adjustment for volume effect (p<0.0001).**

**Our study demonstrated higher hospital MV volume to be independently associated with increased survival among MV patients. Significant differences in outcomes persisted between centres after adjustment for hospital MV volume, supporting a role for other significant determinants of the centre effect.**

KEYWORDS: **Acute respiratory distress syndrome, databases, factual, intensive care unit, outcome assessment, performance, quality of healthcare**

Over the last two decades, advances in the evaluation of healthcare outcomes have shed light on the determinants of survival in patients undergoing various medical and surgical procedures [1–5]. Variations in outcomes are generally believed to stem from differences between institutions, patient characteristics, case mix or organisational factors [3, 4, 6, 7]. Among the factors that lead to differences between institutions (the centre effect), procedure volume, defined as the number of patients receiving a specific procedure in the hospital each year, has been identified as playing a major role [8–12].

Identifying the determinants of the centre effect may suggest means of improving the quality of care [4]. For instance, staffing differences contribute to the centre effect, and the Leapfrog Group has estimated that applying intensive care unit (ICU) physician staffing standards might save >54,000 lives·yr$^{-1}$ [13]. Thus, comparing quantitative performance across institutions may help us to understand how structure and care processes affect patient survival [1, 14, 15].

Acute respiratory failure is common in patients admitted to the ICU [16]. Despite the advances achieved over the last decade, survival has not substantially improved among patients who receive mechanical ventilation (MV) [16, 17]. This fact suggests a need for updating guidelines for MV, and improving the quality and process of care in patients receiving MV. In a large study of 37 acute care hospitals in the USA, the annual volume of patients receiving MV was a major determinant of survival among these patients [11]. However, other studies found no association between volume and outcome, suggesting a need for additional work on larger numbers of patients and hospitals [18–20].

The purpose of this study was to examine the relationship between the number of critically ill

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# Vitamin D status and longitudinal lung function decline in the Lung Health Study

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ABSTRACT: **Low blood vitamin D levels have been postulated to be a risk factor for worse lung function, based largely on cross-sectional data. We sought to use longitudinal data to test the hypothesis that baseline plasma 25-hydroxyvitamin D (25(OH)D) is lower in subjects with more rapid lung function decline, compared to those with slow lung function decline.**

**We conducted a nested, matched case–control study in the Lung Health Study 3 cohort. Cases and controls were continuous smokers with rapid and slow lung function decline, respectively, over ~6 yrs of follow-up. We compared baseline 25(OH)D levels between cases and controls, matching date of phlebotomy and clinical centre.**

**Among 196 subjects, despite rapid and slow decliners experiencing strikingly and significantly different rates of decline of forced expiratory volume in 1 s (-152 *versus* -0.3 mL·yr$^{-1}$; p<0.001), there was no significant difference in baseline 25(OH)D levels (25.0 *versus* 25.9 ng·mL$^{-1}$; p=0.54). There was a high prevalence of vitamin D insufficiency (35%) and deficiency (31%); only 4% had a normal 25(OH)D level in the winter.**

**Although vitamin D insufficiency and deficiency are common among continuous smokers with established mild-to-moderate chronic obstructive pulmonary disease, baseline 25(OH)D levels are not predictive of subsequent lung function decline.**

KEYWORDS: **Chronic obstructive pulmonary disease, smoking, spirometry, vitamin D**

Data from the Third National Health and Nutrition Examination Survey (NHANES III) showed that in a cross-sectional sample of a general US population (n=14,076), lower serum vitamin D levels were associated with lower forced expiratory volume in 1 s ($FEV_1$) in a graded, "dose-dependent" fashion [1]. The results of this report from BLACK and SCRAGG [1] have spurred the hypothesis that low vitamin D levels may be a modifiable risk factor for impaired lung function and chronic obstructive pulmonary disease (COPD).

Vitamin D has long been recognised for its effects on calcium homeostasis and skeletal health. However, its nonskeletal effects have recently received increasing scientific attention, including hypotheses on its potentially beneficial effects in patients with COPD [2]. The mechanisms by which vitamin D levels might affect lung function are unclear. Potential explanations include effects on respiratory infection risk (*via* both innate and adaptive mechanisms) and lung tissue remodelling (*via* matrix metalloproteinases and other pathways) [2–5].

We sought to build upon the cross-sectional data of BLACK and SCRAGG [1] by using longitudinal data to further investigate vitamin D insufficiency as a risk factor for rapid lung function decline and COPD. We hypothesised that, among persons with mild COPD, those with rapid declines in longitudinal lung function would have lower baseline vitamin D levels compared to persons with minimal declines in longitudinal lung function. We tested this hypothesis with a nested, matched case–control study in the Lung Health Study (LHS) 3 cohort.

## MATERIALS AND METHODS

### *Study subjects*

Participants in this nested, matched case–control study were selected from LHS 3, an observational follow-up study of participants in the LHS trial, a 5-yr, 10-centre, randomised trial of a smoking intervention and bronchodilators [6, 7]. Following the trial, study interventions were stopped, but most participants provided informed consent to participate in LHS 3 and agreed to return to study centres for a single long-term (LT) follow-up visit.

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# Aclidinium inhibits cholinergic and tobacco smoke-induced MUC5AC in human airways

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**ABSTRACT: Mucus hypersecretion and mucin MUC5AC overexpression are pathological features of chronic obstructive pulmonary disease (COPD). This study examines the inhibitory effect of aclidinium, a new long-acting muscarinic antagonist, on MUC5AC expression in human airway epithelial cells.**

**MUC5AC mRNA (RT-PCR) and protein expression (ELISA and immunohistochemistry) were studied in human bronchial tissue and differentiated human airway epithelial cells activated with carbachol (100 μM) or cigarette smoke extract in the absence or presence of aclidinium.**

**Carbachol increased MUC5AC mRNA and protein expression in human bronchus and cultured epithelial cells. Aclidinium inhibited the carbachol-induced MUC5AC mRNA and protein expression with potency (half maximal inhibitory concentration) ~1 nM in human bronchus and cultured airway epithelial cells. AG1478, a selective inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase, inhibited carbachol-induced MUC5AC responses, indicating EGFR transactivation. Aclidinium inhibited carbachol-induced phospho-EGFR and phospho-p44/42 MAPK expression. In cultured airway epithelial cells transfected with small interfering (si)RNA against muscarinic receptor subtypes, siRNA-M3 but not siRNA-M2 blocked carbachol-induced MUC5AC expression. Cigarette smoke-induced MUC5AC upregulation in cultured airway epithelial cells was suppressed by aclidinium.**

**In conclusion, aclidinium decreases carbachol and tobacco smoke-induced MUC5AC overexpression in human airway epithelial cells. This effect may contribute to the clinical efficacy of aclidinium in mucus hypersecretory diseases including COPD.**

**KEYWORDS: Aclidinium, human airway epithelial cells, human isolated bronchus, mucin MUC5AC, muscarinic receptor subtypes, small interfering RNA**

Mucus hypersecretion is an important feature of chronic inflammatory airway diseases such as chronic obstructive pulmonary disease (COPD) and asthma, and contributes to their morbidity and mortality [1]. MUC5AC is the predominant mucin gene expressed in healthy human airway epithelial cells, and its expression is augmented in smokers, COPD patients and asthmatics [2].

COPD and asthma are associated with increased pulmonary vagal activity [3]. Muscarinic antagonists are effective drugs for the treatment of COPD and certain forms of asthma, because they exert an anticholinergic effect that results in relaxation of airway smooth muscle [4]. Furthermore, there is recent awareness of the existence of a non-neuronal cholinergic system in humans. Airway epithelial cells are endowed with this system, which represents a previously unappreciated regulatory pathway in pulmonary inflammation and remodelling [5]. Dysfunction of the non-neuronal cholinergic system appears to be involved in the pathophysiology of asthma and COPD [6]. Therefore, these potential anti-inflammatory and anti-remodelling effects of the muscarinic antagonists shown in animal models [7] may be of added value to their established bronchodilation in the management of chronic respiratory diseases.

Aclidinium is a novel, long-acting, muscarinic antagonist that has reached phase III clinical development for COPD treatment [8]. In preclinical studies, aclidinium demonstrated potent muscarinic antagonist activity, comparable to ipratropium and tiotropium, and long duration of action [9]. The aim of the present study was to

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# Candidate genes for COPD in two large data sets

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**ABSTRACT: Lack of reproducibility of findings has been a criticism of genetic association studies on complex diseases, such as chronic obstructive pulmonary disease (COPD).**

**We selected 257 polymorphisms of 16 genes with reported or potential relationships to COPD and genotyped these variants in a case–control study that included 953 COPD cases and 956 control subjects. We explored the association of these polymorphisms to three COPD phenotypes: a COPD binary phenotype and two quantitative traits (post-bronchodilator forced expiratory volume in 1 s ($FEV_1$) % predicted and $FEV_1$/forced vital capacity (FVC)). The polymorphisms significantly associated to these phenotypes in this first study were tested in a second, family-based study that included 635 pedigrees with 1,910 individuals.**

**Significant associations to the binary COPD phenotype in both populations were seen for *STAT1* (rs13010343) and *NFKBIB/SIRT2* (rs2241704) ($p<0.05$). Single-nucleotide polymorphisms rs17467825 and rs1155563 of the *GC* gene were significantly associated with $FEV_1$ % predicted and $FEV_1$/FVC, respectively, in both populations ($p<0.05$).**

**This study has replicated associations to COPD phenotypes in the *STAT1*, *NFKBIB/SIRT2* and *GC* genes in two independent populations, the associations of the former two genes representing novel findings.**

**KEYWORDS: Chronic obstructive pulmonary disease, genetic association, replication, smoking**

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The prevalence of chronic obstructive pulmonary disease (COPD) in Western Europe is ~10% [1], and COPD is expected to be the third most significant cause of death worldwide by 2020 [2]. The most important risk factor for COPD is smoking and there is a dose–response relationship between smoking exposure and reduced lung function, although there is a substantial heterogeneity in the degree of lung function impairment [3]. Only a subset of smokers develops an accelerated rate of decline in lung function that leads to COPD. In addition, there appears to be familial clustering of both impaired lung function and COPD [4]. These insights suggest that susceptibility to COPD may be influenced by genetic factors. The only well-established genetic cause of COPD, $\alpha_1$-antitrypsin deficiency, is present in only 1–2% of individuals with COPD [5]. A number of studies have been performed to find other genetic susceptibility factors for COPD. So far, hundreds of candidate genes have been tested. To date, it has been difficult to replicate genetic findings from one COPD study to another [6]. There may be several explanations for this lack of reproducibility, including small sample sizes, lack of Hardy–Weinberg equilibrium (HWE), poor phenotype characterisation of the COPD cases and genetic heterogeneity [7]. It is now recommended that the findings of a genetic association should be replicated in another sample before being published [7]; nevertheless, only a minority of genetic COPD studies meets this requirement.

To obtain further insight into the genetic basis of COPD, we replicated the relationships of a number of potential COPD candidate genes in two large, independent and well-characterised populations. We selected 257 single-nucleotide polymorphisms (SNPs) in 16 genes based on reported or potential relationships to COPD. They were analysed in a case–control sample from Bergen, Norway, including 953 COPD cases and 956 controls [8]. SNPs with significant associations to COPD were then tested using family-based association analysis in 635 pedigrees with 1,910

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# Prognostic value of procalcitonin in community-acquired pneumonia

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ABSTRACT: The prognostic value of procalcitonin (PCT) levels to predict mortality and other adverse events in community-acquired pneumonia (CAP) remains undefined.

We assessed the performance of PCT overall, stratified into four predefined procalcitonin tiers (<0.1, 0.1–0.25, >0.25–0.5, >0.5 $\mu g \cdot L^{-1}$) and stratified by Pneumonia Severity Index (PSI) and CURB-65 (confusion, urea >7 $mmol \cdot L^{-1}$, respiratory frequency ⩾30 $breaths \cdot min^{-1}$, systolic blood pressure <90 mmHg or diastolic blood pressure ⩽60 mmHg, and age ⩾65 yrs) risk classes to predict all-cause mortality and adverse events within 30 days follow-up in 925 CAP patients.

In receiver operating characteristic curves, initial PCT levels performed only moderately for mortality prediction (area under the curve (AUC) 0.60) and did not improve clinical risk scores. Follow-up measurements on days 3, 5 and 7 showed better prognostic performance (AUCs 0.61, 0.68 and 0.73). For prediction of adverse events, the AUC was 0.66 and PCT significantly improved the PSI (from 0.67 to 0.71) and the CURB-65 (from 0.64 to 0.70). In Kaplan–Meier curves, PCT tiers significantly separated patients within PSI and CURB-65 risk classes for adverse events prediction, but not for mortality. Reclassification analysis confirmed the added value of PCT for adverse event prediction, but not mortality.

Initial PCT levels provide only moderate prognostic information concerning mortality risk and did not improve clinical risk scores. However, PCT was helpful during follow-up and for prediction of adverse events and, thereby, improved the PSI and CURB65 scores.

KEYWORDS: CURB65, mortality, pneumonia, Pneumonia Severity Index, procalcitonin

Assessment of disease severity and prediction of outcome are prerequisites for adequate allocation of healthcare resources and therapeutic options in the management of community-acquired pneumonia (CAP). This includes decisions regarding hospital or intensive care admission, diagnostic work-up, route of antimicrobial therapy and evaluation for early discharge. To optimise and to reduce unnecessary hospital admission rates, professional organisations have developed prediction rules and propagated guidelines to stratify patients with CAP based on predicted risk for mortality [1, 2]. The Pneumonia Severity Index (PSI) is a well-validated scoring system that assesses the risk of death in a two-step algorithm [3]. The tool was developed to identify patient at low risk for mortality [3]. However, it is complex and strongly dependent on age, limiting its general implementation in routine care. The less complex CURB65 (confusion, urea >7 $mmol \cdot L^{-1}$, respiratory frequency ⩾30 $breaths \cdot min^{-1}$, low blood pressure (systolic value <90 mmHg or diastolic value ⩽60 mmHg) and age ⩾65 yrs) score, focuses on five predictors [4]. This score is easier to calculate, but has a slightly inferior prognostic accuracy. Both risk scores were validated for the prediction of mortality only, and their ability to predict other CAP-associated adverse outcomes is not validated. Both scores have limitations for clinical use, including practicability, risk of miscalibration, and only moderate sensitivity and specificity, which leads to hospitalisation of patients where outpatient treatment would have been preferable [5]. Thus, additional risk factors and prognostic biomarkers potentially enhance the prognostic performance of these established risk scores in CAP patients.

Previous studies investigated the prognostic potential of procalcitonin (PCT) for mortality prediction [6]. While studies in the intensive care unit (ICU) setting [7, 8] and in high-risk patients

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# Symptom variability in patients with severe COPD: a pan-European cross-sectional study

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ABSTRACT: In between exacerbations, chronic obstructive pulmonary disease (COPD) is usually regarded as a stable condition, but there is increasing recognition of variability in this state. This cross-sectional study assessed patients' perception of symptom variability.

Participants were outpatients >45 yrs old with COPD, current or ex-smokers, forced expiratory volume in 1 s ($FEV_1$) <50% predicted, $FEV_1$/forced vital capacity <0.7 and no exacerbation leading to therapeutic intervention in the previous 3 months. Patients' perceptions of COPD symptoms and their impact on daily life activities were recorded. Alterations in therapy use in response to COPD worsening were also recorded.

COPD symptoms were experienced by 2,258 (92.5%) out of 2,441 patients during the 7 days before interview. Breathlessness was the most common symptom (72.5%). Daily and/or weekly symptom variability was reported by 62.7% of symptomatic patients; the morning was the worst time of day. Factors associated with perception of variability of breathlessness included younger age, symptom severity and recruitment to the study by general practitioners. The perception of variability was significantly different between European countries or regions.

Patient-perceived COPD symptoms vary over the day and the week, and impact on daily activities; morning being the worst time of day. The majority of patients appear not to adjust treatment when symptoms worsen.

KEYWORDS: Breathlessness, chronic obstructive pulmonary disease, symptoms, symptom variability, treatment

The most common symptoms of chronic obstructive pulmonary disease (COPD) are chronic cough, breathlessness, sputum production, wheezing and chest tightness [1].

Circadian variation of symptoms and lung function is a well known feature of asthma [2–4]. Circadian variations in lung function have also been described in patients with stable COPD, but have received considerably less attention [5–8]. COPD symptoms such as breathlessness are typically described as "characteristically persistent and progressive" [1]. Patients report that they are most fearful of COPD exacerbations and needing care from others. However, in between exacerbations they also experience "good days and bad days" [1, 5]. Several studies have been undertaken to quantify the impact of the disease on daily life and well-being according to symptoms, severity, exacerbation state, emotional state or patients' perceptions of their physical function [5, 9–19]. Even though these studies have described fluctuations of COPD symptoms in individuals over a day, from day to day, and over longer periods of time [20–22], no published study has investigated symptom variability within a large group of COPD patients. This study describes patient perceptions of COPD symptom variability throughout the day, week and year in a large cohort of outpatients.

## METHODS

### Patients

This pan-European, cross-sectional, observational study was conducted in 17 countries: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, Turkey and the UK (NCT00722267). The study was

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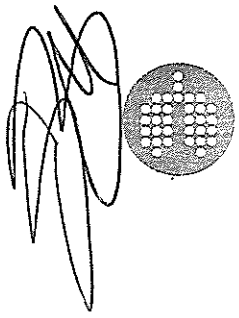

# Once-daily indacaterol *versus* twice-daily salmeterol for COPD: a placebo-controlled comparison

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ABSTRACT: **Indacaterol is a novel, inhaled, once-daily, ultra-long-acting $\beta_2$-agonist bronchodilator recently approved in Europe for the treatment of chronic obstructive pulmonary disease (COPD). The aim of the present study was to investigate the efficacy and safety of indacaterol compared with placebo and the twice-daily $\beta_2$-agonist, salmeterol, as an active control.**

**Patients with moderate-to-severe COPD were randomised to 6 months double-blind treatment with indacaterol (150 μg once daily), salmeterol (50 μg twice daily) or placebo. The primary efficacy end-point was trough (24 h post-dose) forced expiratory volume in 1 s ($FEV_1$) after 12 weeks.**

**1,002 patients were randomised and 838 (84%) completed the study. Indacaterol increased trough $FEV_1$ at week 12 by 170 mL over placebo ($p<0.001$) and by 60 mL over salmeterol ($p<0.001$). Both active treatments improved health status (St George's Respiratory Questionnaire) and dyspnoea (transition dyspnoea index) compared with placebo, with differences between them favouring indacaterol. Safety profiles were similar across the treatment groups, and both indacaterol and salmeterol were well tolerated.**

**Once-daily treatment with 150 μg indacaterol had a significant and clinically relevant bronchodilator effect over 24 h post-dose and improved health status and dyspnoea to a greater extent than twice-daily 50 μg salmeterol. Indacaterol should prove a useful additional treatment for patients with COPD.**

KEYWORDS: **Bronchodilator, chronic obstructive pulmonary disease, clinical trial, indacaterol, salmeterol**

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Chronic obstructive pulmonary disease (COPD) is estimated to affect 10% of the world's population aged ⩾40 yrs, and prevalence is expected to continue to increase over coming years [1, 2]. Regular treatment with one or more long-acting inhaled bronchodilators is an important and recommended element in managing the symptoms of patients with COPD [3]. These agents are administered twice daily (the $\beta_2$-agonists formoterol and salmeterol) or once daily (the anticholinergic tiotropium). Indacaterol is an inhaled ultra-long-acting $\beta_2$-agonist bronchodilator that has demonstrated 24-h efficacy on once-daily administration, and was recently approved in the EU at two doses, 150 and 300 μg once daily, for use in the maintenance treatment of patients with COPD.

In deciding whether to use a new agent, it is clearly useful to know how the efficacy and safety of indacaterol compare with other long-acting bronchodilators using studies of suitable design and appropriate duration. The present study is one of a series designed to compare indacaterol with currently available long-acting bronchodilators. The other studies were a 6-month comparison of indacaterol (150 and 300 μg) with tiotropium [4] and a 1-yr comparison of indacaterol (300 μg) with formoterol [5]. The present study compares indacaterol (150 μg once daily) with salmeterol (50 μg twice daily) over 6 months.

## METHODS

The study was approved by the ethics committees or institutional review boards of participating centres and was conducted in respiratory outpatient clinics, physicians' offices and clinical research centres.

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# Health-related quality of life and functional status in end-stage COPD: a longitudinal study

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ABSTRACT: **Since there is still a dearth of information about the end stage of chronic obstructive pulmonary disease (COPD), the main aim of this study was to examine the development of health-related quality of life (HRQoL) and functional status over time in COPD patients in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV.**

**82 Dutch COPD patients completed the St George's Respiratory Questionnaire (SGRQ) for HRQoL and the Groningen Activities for Daily Living Restriction Scale (GARS) for functional status every 3 months during the year following enrolment. Survival was followed up to 5 yrs after enrolment. Data were analysed by stratifying the study population into severity subgroups according to the lowest, intermediate and highest tertile of SGRQ and GARS at baseline. Outcome measures were change in SGRQ and GARS scores over time and survival time.**

**In the majority of patients, scores on the SGRQ and GARS declined gradually over time. In the subgroup of 32 patients that died within 2 yrs of enrolment, these scores also declined gradually, without steep deteriorations.**

**In patients with end-stage COPD, HRQoL and functional status deteriorated gradually over time, indicating that clinicians did not gain much additional support for differentiating the end stage of COPD by considering HRQoL and functional status using the SGRQ and GARS.**

KEYWORDS: **Activities of daily living, chronic obstructive pulmonary disease, longitudinal studies, palliative care, quality of life**

Chronic obstructive pulmonary disease (COPD) is one of the most important causes of morbidity and mortality worldwide [1, 2]. COPD is a progressive illness, characterised by acute episodes of ill health (exacerbations). Although it is well known that COPD is a potentially fatal disease, there is still a dearth of information about the end stage of the disease. Patients in the end stage of COPD usually experience and survive several severe exacerbations, but any one may prove to be the fatal one [3, 4]. Therefore, the end stage of COPD is hard to define [5, 6]. Because of this unpredictable trajectory of the end stage of COPD, patient–physician communication about palliative and end-of-life care is unlikely to occur [7–9] and, as a consequence, the death of a COPD patient may feel sudden and unexpected for both patients and family members [10].

Studies on the final years of patients with advanced COPD have shown that these are characterised by uncontrolled symptoms, such as intolerable dyspnoea [10–14], and high levels of anxiety [10, 14, 15], depression [10, 14, 16] and social isolation [13, 17, 18]. It is also known that, despite these uncontrolled symptoms, patients in the end stage of COPD have limited access to specific palliative care services when compared to, for example, patients suffering from advanced lung cancer [11, 19, 20]. Cross-sectional studies have shown that health-related quality of life (HRQoL) is low in these patients, even compared to advanced lung cancer patients [11, 19, 21]. CLAESSENS *et al.* [20] state, in their report on the results of the Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatments (SUPPORT), that despite similar preferences about end-of-life care, hospitalised patients with COPD were more likely to have mechanical ventilation, tube feeding and cardiopulmonary resuscitation, compared with patients with lung cancer. It is thus recognised that patients in the end stage of COPD have care needs that are not currently being met [11, 18, 22].

A few studies have examined the course of HRQoL by using longitudinal measures [23, 24]. These studies, however, focused on patients with

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# Significant increase of CD57$^+$ cells in pulmonary lymphoid follicles of COPD patients

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ABSTRACT: **Although the presence of pulmonary lymphoid follicles (LFs) has been associated with the progression of chronic obstructive pulmonary disease (COPD), there is no information regarding the pattern of vascularisation, expression of addressins or inflammatory cell densities within these structures in COPD.**

**Histological and immunohistochemical techniques were used to assess the prevalence, structure, localisation, vascularisation and cell proliferation/apoptosis of LFs, as well as the follicular density of B- and T-lymphocytes, macrophages, dendritic cells and CD57$^+$ cells, in lung tissue of nine nonsmokers, 18 smokers without COPD, 16 smokers with moderate COPD and 16 patients with very severe COPD.**

**The density of CD57$^+$ cells within LFs of COPD patients was significantly increased compared to that of nonsmokers and smokers without COPD ($p<0.05$). Moreover, the percentage of LF profiles with cell apoptosis was also significantly higher in COPD patients ($p=0.03$). By contrast, no significant differences among groups were observed in the follicular densities of other inflammatory cells, nor in the distribution of blood and lymphatic vessels within LFs.**

**Since CD57$^+$ cells are important effectors of cytotoxicity and immune regulation, an increase in their follicular density supports the hypothesis of local immune dysfunction in COPD.**

KEYWORDS: **Cigarette smoking, follicles, immunohistochemistry, lung inflammation**

Chronic obstructive pulmonary disease (COPD) is characterised by progressive and not fully reversible airflow limitation, associated with an abnormal inflammatory response of the lung to noxious particles and gases, mainly cigarette smoke [1]. The main pathological features of COPD are found in both peripheral airways and lung parenchyma, as well as in pulmonary vasculature.

It is now established that COPD is a chronic inflammatory condition resulting from complex interactions between cells belonging to the innate and adaptive immune systems. Recently, this inflammatory process has been associated with the development of ectopic lymphoid follicles (LFs) in lungs of COPD patients [2–7], which are similar to the tertiary lymphoid tissue found in other inflammatory or autoimmune diseases [8, 9].

Since LFs were described in the airways of COPD patients [2], increasing attention has been focused on the study of these structures and their possible role in the pathogenesis of COPD. Progression of COPD from Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 0 to stage 4 is associated with the number of bronchioles containing LFs [3]. Furthermore, although the nature of the stimuli that trigger the formation of LFs remains unknown, an oligoclonal process in follicular B-lymphocytes of COPD patients and mice with emphysema has been reported, which suggests an antigen-specific proliferation in these structures [4].

Conversely, despite increased numbers of macrophages, dendritic cells, natural killer cells and lymphocytes having been reported in lung tissue of COPD patients [10, 11], few data are available on the follicular densities of these cells and the molecules involved in their recruitment to LFs in COPD, especially at the most severe stages of the disease. Indeed, only one study reported a higher percentage of T-regulatory cells within LFs of moderate COPD patients compared with smokers and nonsmokers [5], but no information is available regarding vascular supply, lymphatic drainage or the follicular densities of other key inflammatory cells in subjects with and without COPD. Moreover, there

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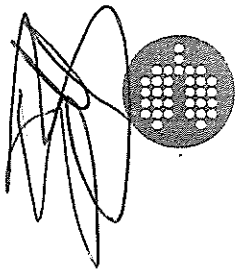

# Lung exposure to nanoparticles modulates an asthmatic response in a mouse model

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**ABSTRACT: The aim of this study was to investigate the modulation of an asthmatic response by titanium dioxide ($TiO_2$) or gold (Au) nanoparticles (NPs) in a murine model of diisocyanate-induced asthma.**

**On days 1 and 8, BALB/c mice received 0.3% toluene diisocyanate (TDI) or the vehicle acetone–olive oil (AOO) on the dorsum of both ears (20 μL). On day 14, the mice were oropharyngeally dosed with 40 μL of a NP suspension (0.4 $mg \cdot mL^{-1}$ (~0.8 $mg \cdot kg^{-1}$) $TiO_2$ or Au). 1 day later (day 15), the mice received an oropharyngeal challenge with 0.01% TDI (20 μL). On day 16, airway hyperreactivity (AHR), bronchoalveolar lavage (BAL) cell and cytokine analysis, lung histology, and total serum immunoglobulin E were assessed.**

**NP exposure in sensitised mice led to a two- ($TiO_2$) or three-fold (Au) increase in AHR, and a three- ($TiO_2$) or five-fold (Au) increase in BAL total cell counts, mainly comprising neutrophils and macrophages. The NPs taken up by BAL macrophages were identified by energy dispersive X-ray spectroscopy. Histological analysis revealed increased oedema, epithelial damage and inflammation.**

**In conclusion, these results show that a low, intrapulmonary doses of $TiO_2$ or Au NPs can aggravate pulmonary inflammation and AHR in a mouse model of diisocyanate-induced asthma.**

**KEYWORDS: Diisocyanate-induced asthma, gold, nanoparticle, titanium dioxide, toluene diisocyanate**

Occupational asthma accounts for an important percentage of work-related respiratory illnesses [1]. It has been reported that at least 9–15% cases of asthma in adults are due to occupational exposures [2]. Isocyanates are widely used in various industrial and consumer products, and they are a major cause of chemical-induced occupational asthma throughout the world [3].

We have previously described a mouse model of chemical-induced asthma using toluene diisocyanate (TDI) as sensitising agent [4–6]. In this mouse model, we initiate sensitisation *via* dermal application, which is followed by a single airway challenge, resulting in asthma-like responses. In obstructive asthma, it is generally assumed that exposure in the respiratory tract is the key route and site for the initiation of the immune responses. However, despite reductions in workplace respiratory exposures, isocyanate asthma continues to occur, and this has prompted a focus on skin as a route of exposure [3, 7–9]. Recently, several animal models have shown convincingly that skin exposure to chemical sensitisers (predominantly isocyanates, but also anhydrides and persulfate salts) can induce systemic sensitisation, which may result in asthma-like respiratory responses when the animal is later challenged *via* the airways [5, 10–12].

Current estimates indicate that >800 nanomaterial-containing products are commercially available, according to the Woodrow Wilson Database [13]. These nanomaterials can affect health through consumer products, and occupational and environmental exposures [14, 15]. Both titanium dioxide ($TiO_2$) and gold (Au) nanoparticles (NPs) are produced and used in substantial quantities, and pose an emergent occupational and consumer risk [13]. $TiO_2$ NPs are one of the most abundantly produced and widely utilised nanomaterials [16], with applications in sunscreens, cosmetics, tooth pastes and food products [17, 18]. The biological

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# A mobile telephone-based interactive self-care system improves asthma control

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ABSTRACT: The self-management of asthma can improve clinical outcomes. Recently, mobile telephones have been widely used as an efficient, instant personal communication tool. This study investigated whether a self-care system will achieve better asthma control through a mobile telephone-based interactive programme.

This was a prospective, controlled study in outpatient clinics. From 120 consecutive patients with moderate-to-severe persistent asthma, 89 were eventually recruited for the study, with 43 in the mobile telephone group (with a mobile telephone-based interactive asthma self-care system).

In the mobile telephone group, mean±SEM peak expiratory flow rate significantly increased at 4 (378.2±9.3 L·min$^{-1}$; n=43; p=0.020), 5 (378.2±9.2 L·min$^{-1}$; n=43; p=0.008) and 6 months (382.7±8.6 L·min$^{-1}$; n=43; p=0.001) compared to the control group. Mean±SEM forced expiratory volume in 1 s significantly increased at 6 months (65.2±3.2% predicted; n=43; p<0.05). Patients in the mobile telephone group had better quality of life after 3 months, as determined using the Short Form-12® physical component score, and fewer episodes of exacerbation and unscheduled visits than the control group. Patients in the mobile telephone group significantly increased their mean daily dose of either systemic or inhaled corticosteroids compared with the control group.

The mobile telephone-based interactive self-care system provides a convenient and practical self-monitoring and -management of asthma, and improves asthma control.

KEYWORDS: Asthma control, interactive, mobile telephone, self-care system, telemedicine

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Worldwide asthma prevalence has increased very considerably in recent decades [1, 2]. The prevalence rate of adult bronchial asthma in Taipei City, Taiwan is 7.8%, and its morbidity and mortality are a distinct social burden not only for patients, but also for society in general [3]. Common problems in asthma care in Taiwan and, perhaps, globally include patients seeking treatment only for acute asthma attacks, lack of concepts of long-term asthma care, poor compliance with inhaled medication, monitoring and assessment of asthma severity by symptoms and signs only, shortage of time and personnel to educate patients, and lack of objective asthma assessment [4–9].

Asthma is better controlled if patients self-monitor their symptoms and peak flow, follow a written action plan, and regularly visit their physician [10]. However, a written action plan may be not comprehensive enough to provide guided self-management for all asthma events that happen at home. Short Message Service (SMS), a convenient, reliable, affordable and secure means of telemedicine, has been shown to improve asthma control when added to a written action plan and standard follow-up [11]. Recently, a systemic review of home telemonitoring for patients with respiratory conditions, particularly when evaluated in randomised controlled trials in asthma, showed that home telemonitoring of respiratory conditions results in early identification of deteriorations in patient condition and symptom control [12–17]. In Taiwan, an internet-based asthma telemonitoring programme reportedly increased self-management skills and improved asthma outcomes, and appeared to be an effective technology for care that is well accepted by asthmatic children and their caregivers [13]. However, telephone communication is time-consuming and staff-heavy, while internet access is not always convenient.

Mobile telephones are widely used as an efficient, instant personal communication tool, such that their function has been expanded from a simple telephone to a microcomputer. General Packer Radio Service (GPRS) is now a common function of all makes of cell phones. Through GPRS, many

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# Exercise is associated with improved asthma control in adults

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ABSTRACT: **Global asthma control levels are suboptimal. The influence of regular exercise on asthma control is unclear.**

**We assessed the effects of a 12-week supervised exercise intervention followed by 12 weeks of self-administered exercise on adults with partially controlled asthma (n=21) and matched controls (n=15). Assessments were conducted at baseline and week 12 for both the exercise and control group, and again at week 24 for the exercise group.**

**There was a significant treatment effect on asthma control in the exercise group, as measured by the Asthma Control Questionnaire (ACQ), from baseline to week 12, compared with the control group. A clinically significant improvement (0.5 increase in ACQ score) was observed for asthma quality of life and ACQ in the exercise group from baseline to week 12. There was a significant improvement in aerobic fitness from baseline to week 24 in the exercise group.**

**In conclusion, a 12-week supervised exercise intervention led to improvements in asthma control and quality of life in partially controlled asthmatics motivated to exercise. These improvements were maintained, while aerobic fitness and perceived asthma control significantly improved over an additional 12 weeks of self-administered exercise. These findings indicate that a structured exercise intervention can improve asthma control.**

KEYWORDS: **Aerobic fitness, asthma, exercise, perceived asthma control, quality of life**

There is no known cure for asthma [1, 2]; however, pharmacological intervention has been shown to significantly improve symptoms [3–5]. The use of inhaled corticosteroids, long acting $\beta_2$-agonists and a combination of these medications have been shown to improve asthma control [3, 4], but compliance rates of >80% are required to maintain this level of control [6]. Unfortunately, compliance to asthma treatment in countries where treatment is readily accessible remains poor [7, 8].

Asthma control is determined by the frequency of daytime symptoms, limitation of activities, nocturnal symptoms, need for reliever medication, lung function and exacerbations [1]. Accordingly, patients are classified as having controlled, partially controlled or uncontrolled asthma. Recent data show that only 23% of asthmatics are controlled [9] and, despite receiving specialist care, 50% are not well controlled [8]. Poor asthma control has been associated with more emergency room visits, physician visits and days spent in hospital [10].

Recent research demonstrates that healthcare use is higher in physically inactive asthmatics compared with physically active asthmatics [11]. This finding suggests that active asthmatics have better asthma control, if healthcare use is a proxy of asthma control. Exercise interventions involving adults with asthma have shown improvements in measures such as lung function [12], quality of life [13], breathlessness [14, 15] and controller therapy [16], while animal models have shown improvements in airway inflammation [17, 18]. However, a direct association between asthma control and exercise has not yet been made.

VOLLMER *et al.* [19] reported that the activity limitation component, which includes both physical and nonphysical activity, is the most powerful contributor to asthma control, suggesting that improvements in aerobic fitness may improve control in partially controlled but physically inactive asthmatics. To date, the benefits of exercise interventions have been demonstrated by medically supervised programmes [16, 20]. The effects of such programmes on future physical activity habits are unclear; furthermore, the effects of self-administered exercise programmes remain unknown. Self-administered exercise may be a more cost-effective and readily available therapy for the general population of adults with asthma. If exercise positively impacts asthma control, it may be an important adjunct

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# Combined exposure to dog and indoor pollution: incident asthma in a high-risk birth cohort

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ABSTRACT: **The impact of single exposures on asthma development is better understood than the effect of multiple exposures. The objective of the present study was to evaluate the effect of combined early exposure to dog allergen (Can-f1) plus indoor nitrogen dioxide ($NO_2$) or environmental tobacco smoke (ETS) on asthma and bronchial hyperreactivity (BHR) in a high-risk birth cohort. We also aimed to assess atopy's impact on the effects of these exposures.**

**Peri-birth ETS exposure was measured using cord blood cotinine (CCot). During year 1, atopy, $NO_2$, Can-f1, and urinary cotinine (UCot) were measured. At 7 yrs of age, 380 children were assessed for asthma and BHR. Exposure effects were determined using stepwise multiple linear regression.**

**Co-exposure to elevated Can-f1 and $NO_2$, or Can-f1 and ETS (CCot), increased risk for asthma, relative to having neither such exposure (OR 4.8 (95% CI 1.1–21.5) and 2.7 (1.1–7.1), respectively); similar risks resulted when substituting dog ownership for allergen. Atopy increased asthma and BHR risk associated with several exposures; notably, atopy with elevated UCot, relative to atopy without such exposure, increased risk of BHR (OR 3.1 (95% CI 1.1–8.6)).**

**In a high-risk birth cohort, early co-exposure to Can-f1 and $NO_2$ or ETS increased the risk of incident asthma. Atopy increased the risk of asthma and BHR associated with ETS.**

KEYWORDS: **Asthma, atopy, dog, environmental tobacco smoke, nitrogen dioxide**

Childhood asthma is common and childhood allergic diseases have increased significantly in recent decades [1]. While it appears that exposure to allergens often promotes allergen sensitisation [2], the role of allergen exposure in asthma initiation is still controversial [2, 3], and there is evidence that environmental pollutants and respiratory infections are influential in the development of asthma.

Many studies have focused on asthma risks for single factors such as environmental tobacco smoke (ETS) [4] and nitrogen dioxide ($NO_2$) [5], yet multiple exposures are realistically experienced. There is increasing interest in how interactions between air pollutants and allergens promote the development of respiratory disease in childhood [6].

Most of the evidence supporting air pollutants' interaction with allergens has come from *in vitro* or animal studies [3, 7]. For example, a study using a mouse model suggested that while ovalbumin inhalation alone was insufficient to trigger the innate immune response, $NO_2$ along with ovalbumin could promote allergic sensitisation and development of asthma [7]. In a rare human study addressing such interactions, a significant association between respiratory symptoms (labelled "bronchitic" but consistent with asthma exacerbation) and particulate matter was only noted in the subset of asthmatic children who owned dogs [8]. In another study, the exposure of mild asthmatics to $NO_2$, at concentrations typical of the home environment, enhanced the drop in airflow associated with inhaled allergen [9]. Because it is possible to at least partially remedy dog allergen (Can-f1) and because it is particularly potent in augmenting pollutant effects [8], we focused on this allergen. The end-points chosen were asthma and bronchial hyperreactivity (BHR), the latter having been little-studied in this context in spite of its appeal as a quantitative measure of airway reactivity.

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# Osteopontin expression and relation to disease severity in human asthma

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**ABSTRACT: Recent studies have associated osteopontin (OPN) with allergic inflammation; however, its role in human asthma remains unclear. The aim of this study was to measure OPN levels in the serum, bronchoalveolar lavage fluid (BALF) and bronchial tissue of healthy controls and asthmatics, identify cellular sources of OPN and examine possible correlations between OPN expression, disease severity and airway remodelling.**

**Serum samples were obtained from 35 mild-to-moderate asthmatics, 19 severe asthmatics and 17 healthy controls in the steady state and in cases of exacerbation. Of these subjects, 29 asthmatics and nine controls underwent bronchoscopy with endobronchial biopsy and BALF collection. OPN expression was determined by ELISA and immunohistochemistry/immunofluorescence. Reticular basement membrane thickness and goblet cell hyperplasia were also determined.**

**Serum and BALF OPN levels were significantly increased in all asthmatics in the steady state, whereas serum levels decreased during exacerbations. OPN was upregulated in the bronchial tissue of all patients, and expressed by epithelial, airway and vascular smooth muscle cells, myofibroblasts, T-lymphocytes and mast cells. OPN expression correlated with reticular basement membrane thickness and was more prominent in subepithelial inflammatory cells in severe compared to mild-to-moderate asthma.**

**OPN expression is upregulated in human asthma and associated with remodelling changes, and its subepithelial expression correlates with disease severity.**

**KEYWORDS: Airway remodelling, allergic inflammation, asthma, basement membrane, osteopontin, research bronchoscopy**

41.

Asthma is an inflammatory disorder of the conducting airways, typically associated with aberrant type-2 T-helper cell (Th2) activation and response against environmental antigens. Airway inflammation in asthma is a multicellular process that is associated with structural alterations of the airway components, a process known as airway remodelling [1]. The prominent role of airway inflammation and remodelling in the pathogenesis and clinical presentation of asthma has led to the current focus on mediators potentially involved in both processes.

Osteopontin (OPN) is a cytokine, originally described as a structural component of the extracellular matrix, that has the ability to bind to proteins and most types of collagen [2]. OPN exists in a secreted form that mediates cell adhesion, migration and survival [3], and an intracellular nonsecreted form [4]. OPN is produced by most cells of the immune system, including T-cells, B-cells, macrophages, neutrophils, eosinophils, natural killer cells and mast cells, as well as structural cells, including fibroblasts and smooth muscle and epithelial cells [5, 6]. OPN has been typically classified as a type-1 cytokine [7]. In humans, increased OPN expression has been observed in a number of Th1-mediated lung diseases, including granulomatous diseases and pulmonary fibrosis [8, 9].

There is now, also, emerging evidence to support an active role for OPN in Th2-linked inflammation and remodelling. OPN expression is upregulated in nasal tissue samples taken from asthmatic patients with chronic rhinosinusitis [10], and allergic patients undergoing successful long-term venom allergen immunotherapy show increased levels of serum OPN [11]. Moreover, OPN is expressed and functional in peripheral blood eosinophils of atopic human subjects [12],

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# Increased Rho-kinase expression and activity and pulmonary endothelial dysfunction in smokers with normal lung function

**S. Duong-Quy*, P. Dao*, T. Hua-Huy*, C. Guilluy#, P. Pacaud# and A.T. Dinh-Xuan***

**ABSTRACT: Endothelial dysfunction is one of the main consequences of the toxic effects of cigarette smoke on the vascular system. Increasing evidence suggests that the small G-protein RhoA and its downstream effectors, the Rho-kinases (ROCKs), are involved in systemic endothelial dysfunction induced by cigarette smoke. This study aimed to evaluate the role of the RhoA/ROCKs pathway in pulmonary artery endothelial function in current smokers with normal lung function.**

**Lung tissues were obtained from nonsmokers and smokers who underwent lobectomy for lung carcinoma. Arterial relaxation in response to acetylcholine (ACh) was assessed in isolated pulmonary arterial rings. Protein expressions and activities of endothelial nitric oxide synthase (eNOS), ROCKs and the myosin phosphatase subunit 1 (MYPT-1) were sought.**

**Relaxation in response to ACh was significantly lower in smokers as compared with nonsmokers (n=8 in each group), consistent with reduced eNOS activity in the former compared with the latter. eNOS protein expression remained, however, the same in both groups. Expression of ROCKs, guanosine triphosphate-RhoA and phosphorylated MYPT-1 were significantly increased in smokers compared with controls.**

**Pulmonary endothelial dysfunction is present in smokers whose lung function has not yet been impaired. Reduced activity of eNOS accounts at least in part for this endothelial dysfunction. Increased expression and activity of ROCKs accounts for another part through direct or indirect inhibition of the Rho-A/ROCKs pathway on nitric oxide synthesis and sustained pulmonary vasoconstriction through inhibition of myosin phosphatase.**

**KEYWORDS: Cyclic guanosine monophosphate, endothelial dysfunction, endothelial nitric oxide synthase, RhoA, Rho-kinases, tobacco smoke**

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Tobacco smoke is associated with high mortality and morbidity related to cardiovascular disease [1], and is currently the leading cause of chronic obstructive pulmonary disease (COPD) [2]. The most prominent pathological changes in COPD patients are progressive airflow limitation, peripheral airway inflammation and pulmonary vascular remodelling [3, 4]. Structural changes of the pulmonary vasculature, however, are not exclusive to patients with severe COPD, as they have been found in patients with milder degrees of airway obstruction, and even in heavy smokers without airflow limitation [5]. Together with its deleterious effects on peripheral airways, tobacco smoke also causes systemic endothelial dysfunction in active and passive smokers [6, 7], in whom endothelial dysfunction often precedes structural changes of pulmonary vessels [8, 9].

In smokers, endothelial dysfunction might directly result from the toxic effects of, or be indirectly due to, the release of inflammatory mediators induced by free radicals derived from tobacco smoke [10]. The precise mechanisms of tobacco smoke-related endothelial dysfunction are not fully understood, but it is hypothesised that decreased production or reduced bioavailability of nitric oxide (NO) in the pulmonary vasculature of smokers might be partly implicated [11].

Recent studies suggest that the small G-protein RhoA and its downstream effectors the Rho-kinases (ROCK-1 or ROCK-β and ROCK-2 or

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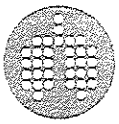

**SERIES "HOT TOPICS IN PAEDIATRIC ASTHMA"**
**Edited by K-H. Carlsen, G. Hedlin and A. Bush**
**Number 5 in this Series**

# Assessment of problematic severe asthma in children

**K.C. Lødrup Carlsen, G. Hedlin, A. Bush, G. Wennergren, F.M. de Benedictis, J.C. De Jongste, E. Baraldi, C. Pedroletti, A. Barbato, K. Malmström, P. Pohunek, S. Pedersen, G.L. Piacentini, R.J.M. Middelveld and K.H. Carlsen on behalf of the PSACI (Problematic Severe Asthma in Childhood Initiative) group**

ABSTRACT: **Assessment of problematic severe asthma in children should be performed in a step-wise manner to ensure an optimal approach. A four-step assessment scheme is proposed. First, a full diagnostic work-up is performed to exclude other diseases which mimic asthma. Secondly, a multi-disciplinary assessment is performed to identify issues that may need attention, including comorbidities. Thirdly, the pattern of inflammation is assessed, and finally steroid responsiveness is documented.**

**Based upon these four steps an optimal individualised treatment plan is developed. In this article the many gaps in our current knowledge in all these steps are highlighted, and recommendations for current clinical practice and future research are made.**

**The lack of good data and the heterogeneity of problematic severe asthma still limit our ability to optimise the management on an individual basis in this small, but challenging group of patients.**

KEYWORDS: **Asthma, child, diagnostics, severe**

Although the majority of children with asthma respond well to standard therapy, a significant proportion [1] still have problematic, severe disease that is not controlled with conventional management. A birth cohort identified 4.5% of the asthmatic children with "severe asthma", whereas others found that 39–55% of children with problematic severe asthma had "difficult to treat" asthma [2, 3]. A recent paper [4], which discussed definitions, classifications and age-related presentation of problematic severe asthma in childhood, suggested asthmatic children warranted further investigation and outlined triggers of asthma exacerbations. It was emphasised that many children may have factors apart from the underlying severity of asthma that contribute to their severe disease, including comorbidities, socio-economic problems, adverse environmental exposures (such as tobacco smoke, relevant allergens and other harmful factors), psychological problems and especially poor adherence to treatment.

Age is relevant not only for the presentation of disease and the underlying pathophysiology, but also for the way the child can be assessed. Our article focuses on age-appropriate assessment methods for which there is a scientific basis, and reports on a step-wise approach to assess diagnostic possibilities, airway inflammation and therapeutic responses to corticosteroids (fig. 1). Essentially, these steps lead to the child being placed in one of four categories: wrong diagnosis ("not asthma"); asthma with significant comorbidities that need to be addressed ("asthma plus"); asthma which is not responding to treatment because the basics have not been got right ("difficult asthma"); and true asthma ("severe, therapy-resistant asthma"). It is patients

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REVIEW

# Circulating endothelial progenitor cells and chronic pulmonary diseases

A. Huertas and P. Palange

ABSTRACT: **Circulating endothelial progenitor cells (EPCs) are bone marrow-derived cells that contribute to vascular healing and remodelling under physiological and pathological conditions. Although controversies exist regarding the definition and origin of EPCs, it has been widely demonstrated that they are involved in several diseases and that they have therapeutic implications.**

**Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation that is not fully reversible, associated with abnormalities of airways (bronchitis) and parenchyma (emphysema), reduced exercise tolerance and systemic inflammation.**

**Growing evidence has also suggested that endothelial dysfunction may play a role in COPD. Although it is not clear whether endothelial dysfunction represents a cause or a consequence of COPD, several studies have highlighted the importance of EPCs in this disease, suggesting that the bone marrow could be a novel target of COPD.**

**The present review summarises the role of EPCs in pulmonary diseases, with particular emphasis on COPD. The aim is to improve understanding as to the possible role of EPCs in COPD pathophysiology. This may help in the identification of novel diagnostic and therapeutic tools in COPD.**

KEYWORDS: **Chronic obstructive pulmonary disease, endothelium**

In 1997, ASAHARA *et al.* [1] first described the differentiation of adult haemopoietic progenitor cells into an endothelial phenotype. In 1998, SHI *et al.* [2] showed that genetically tagged transplanted bone marrow cells were covering implanted grafts. These pioneering studies suggested the presence of circulating angioblasts in the adult peripheral blood. Since the late 1990s, circulating haemopoietic and endothelial progenitor cells (EPCs) have been studied in order to characterise and understand their role in the pathophysiology of various diseases. Accumulating evidence has shown that circulating EPCs contribute to vascular healing and remodelling under physiological and pathological conditions. Despite some controversies still existing with respect to the identification and origin of these progenitor cells, increasing evidence suggests that these bone marrow-derived cells play an important role in diseases, such as cardiovascular and cerebrovascular, endocrinological, haematological and connective tissue disorders [3]. Plasma levels of these circulating EPCs have been seen to correlate with disease severity and risk factors [4]. In contrast to the conventional assumption that damaged organs are repaired only by migration and proliferation of adjacent cells, increasing evidence suggests that ectopic progenitor cells are mobilised into the systemic circulation and recruited to the site of tissue regeneration. Furthermore, EPCs also seem to have therapeutic value in coronary artery diseases, increasing neovascularisation of tissue following ischaemia [5–7] and contributing to re-endothelialisation after endothelial injury [8, 9].

The aims of the present review are, first, to provide a state-of-the-art overview of circulating EPCs and pulmonary diseases, with particular emphasis on chronic obstructive pulmonary disease (COPD) and emphysema, and then to present recent findings in the field, which may have implications for diagnostic tools and novel therapeutic strategies in chronic lung diseases.

## CIRCULATING EPCS

### *Definition*

In 1997, ASAHARA *et al.* [1] showed that purified CD34+ haemopoietic EPCs from human peripheral blood could differentiate into endothelial cells (ECs) *in vitro* [1]. These so-called endothelial

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REVIEW

# Impact of inspiratory muscle training in patients with COPD: what is the evidence?

**R. Gosselink*,#, J. De Vos*,#, S.P. van den Heuvel', J. Segers*,#, M. Decramer*,# and G. Kwakkel+**

ABSTRACT: **A meta-analysis including 32 randomised controlled trials on the effects of inspiratory muscle training (IMT) in chronic obstructive pulmonary disease (COPD) patients was performed. Overall and subgroup analyses with respect to training modality (strength or endurance training, added to general exercise training) and patient characteristics were performed. Significant improvements were found in maximal inspiratory muscle strength ($P_{I,max}$; +13 $cmH_2O$), endurance time (+261 s), 6- or 12-min walking distance (+32 and +85 m respectively) and quality of life (+3.8 units). Dyspnoea was significantly reduced (Borg score -0.9 point; Transitional Dyspnoea Index +2.8 units). Endurance exercise capacity tended to improve, while no effects on maximal exercise capacity were found. Respiratory muscle endurance training revealed no significant effect on $P_{I,max}$, functional exercise capacity and dyspnoea. IMT added to a general exercise programme improved $P_{I,max}$ significantly, while functional exercise capacity tended to increase in patients with inspiratory muscle weakness ($P_{I,max}$ <60 $cmH_2O$).**

**IMT improves inspiratory muscle strength and endurance, functional exercise capacity, dyspnoea and quality of life. Inspiratory muscle endurance training was shown to be less effective than respiratory muscle strength training. In patients with inspiratory muscle weakness, the addition of IMT to a general exercise training program improved $P_{I,max}$ and tended to improve exercise performance.**

KEYWORDS: **Meta-analysis, muscle training, respiratory muscles, systematic review**

Respiratory muscle weakness is observed in chronic obstructive pulmonary disease (COPD) patients [1, 2] and contributes to hypercapnia [3], dyspnoea [4, 5], nocturnal oxygen desaturation [6] and reduced walking distance [7]. During exercise it has been shown that diaphragm work is increased in COPD [8] and COPD patients use a larger proportion of the maximal inspiratory pressure ($P_{I,max}$) than healthy subjects [9]. This pattern of breathing is closely related to the dyspnoea sensation during exercise [9] and might potentially induce respiratory muscle fatigue. However, diaphragmatic fatigue was not demonstrated after exhaustive exercise [10]. Studies in patients with COPD have shown natural adaptations of the diaphragm to greater oxidative capacity and resistance to fatigue [11–13]. The abovementioned considerations gave conflicting arguments to the rationale of respiratory muscle training in COPD. Current guidelines [14, 15] and meta-analyses [16–20] are not undisputedly positive on the application of inspiratory muscle training (IMT). From meta-analyses it is clear that IMT increases inspiratory muscle strength and endurance, and decreases dyspnoea. However, exercise performance and quality of life did not improve significantly [18, 20, 21]. The addition of IMT to a general exercise programme did not improve exercise performance [20]. Furthermore, differences in effects of resistance and endurance training were never analysed, while patient characteristics relevant for favourable effects of IMT have not been identified so far. Finally, many randomised controlled trials have been published since our previous meta-analysis, offering more input for more extensive analysis. The aim of the

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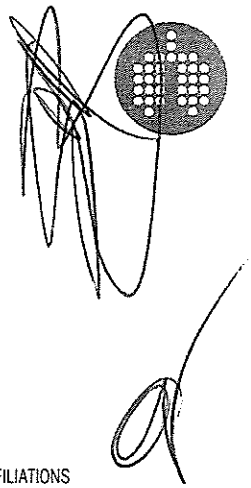

**SERIES "UPDATE ON TUBERCULOSIS"**
**Edited by C. Lange, M. Raviglione, W.W. Yew and G.B. Migliori**
**Number 4 in this Series**

# Treatment of tuberculosis: update 2010

**W.W. Yew*, C. Lange# and C.C. Leung***

**ABSTRACT: Currently, the standard short-course chemotherapy for tuberculosis comprises a 6-month regimen, with a four-drug intensive phase and a two-drug continuation phase. Alternative chemotherapy using more costly and toxic drugs, often for prolonged durations generally >18 months, is required for multidrug-resistant and extensively drug-resistant tuberculosis. Directly observed treatment, as part of a holistic care programme, is a cost-effective strategy to ensure high treatment success and curtail development of drug resistance in tuberculosis. New antituberculosis drugs are urgently needed to improve the present standard short-course and alternative chemotherapies, by shortening administration durations and increasing cure rates, through the greater potency of these agents. At the same time, the role of adjunctive surgery for drug-resistant tuberculosis has to be better defined. Immunotherapy might improve treatment outcomes of both drug-susceptible and -resistant tuberculosis, and warrants further exploration.**

KEYWORDS: Review, tuberculosis, treatment

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In 2008, 11.5 million people were estimated to be living with tuberculosis, with 9.4 million of them having incident disease. Among the 1.9 million people who died of tuberculosis, 0.5 million were seropositive for HIV [1]. While the present chemotherapy for tuberculosis is highly efficacious, it has the disadvantages of being lengthy and complex, and does not live up to the expectation of adequately controlling the current global tuberculosis situation. In 2008, an estimated 390,000–510,000 cases of multidrug-resistant (MDR) tuberculosis with bacillary resistance to at least isoniazid (H) and rifampicin (R) are estimated to emerge every year worldwide, with China and India together accounting for ~50% of this global burden. In 2008, MDR tuberculosis caused an estimated 150,000 deaths [2]. Recently emerging extensively drug-resistant (XDR) tuberculosis is defined as MDR tuberculosis with additional bacillary resistance to any fluoroquinolone and one or more of the three (second-line) injectable drugs: amikacin, capreomycin and kanamycin. Approximately 5.4% of MDR tuberculosis reported worldwide could be categorised as XDR tuberculosis, with the proportion exceeding 10% in some countries [2]. This article examines the current status and future prospects of treatment of tuberculosis. Where appropriate, evidence levels for the recommended treatment regimens and modalities are given in accordance with the grading system of the Scottish Intercollegiate Guidelines Network (see Appendix) [3].

Before discussing recommended drug regimens for treating of pulmonary tuberculosis, an understanding of basic mycobacteriology and antituberculosis drug action would be beneficial.

## SCIENTIFIC BASIS OF SHORT-COURSE CHEMOTHERAPY

*Mycobacterium tuberculosis*, the causative organism of tuberculosis, is a slow-growing bacterium that can also enter a phase of dormancy, which appears to be drug-refractory. Four hypothetical populations of organisms [4] may exist in a patient with tuberculosis: 1) actively growing organisms, usually present in abundance (extracellularly) within aerated cavities; 2) slow, intermittently growing organisms in an unstable part of the lesion; 3) organisms surviving under microaerobic conditions in a low environmental pH, either in inflammatory lesions or within phagolysosomes of macrophages; and 4) completely dormant organisms surviving under anaerobic conditions.

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# Screening for sleep-disordered breathing in neuromuscular disease using a questionnaire for symptoms associated with diaphragm paralysis

**J. Steier*,#, C.J. Jolley*, J. Seymour*, H. Teschler#, Y.M. Luo', M.I. Polkey+ and J. Moxham***

**ABSTRACT: Patients with neuromuscular disease (NMD) are at risk of developing sleep-disordered breathing (SDB) following respiratory muscle involvement. We hypothesised that a questionnaire based on clinical symptoms and signs of diaphragm weakness can be used to screen for SDB in such patients.**

**We developed a self-administered multiple choice questionnaire containing five questions (Sleep-Disordered Breathing in Neuromuscular Disease Questionnaire (SiNQ)-5), scoring 0–10 points. 125 patients were enrolled: 32 with respiratory muscle weakness, 35 subjects with normal respiratory muscle strength and 58 patients with obstructive sleep apnoea (OSA). All subjects underwent full polysomnography.**

**NMD patients with involvement of the respiratory muscles scored mean±SD 6.8±2.3 out of 10 points, significantly higher than both OSA patients 2.5±2.3 and normal subjects 1.0±2.0 ($p<0.001$). A score of five or more points in the SiNQ-5 had a sensitivity of 86.2%, specificity of 88.5%, positive predictive value of 69.4% and a negative predictive value of 95.5% to identify NMD with combined SDB.**

**A short self-administered questionnaire, the SiNQ-5, based on clinical symptoms can reliably screen for SDB in patients with diaphragm weakness. However, comorbidities, such as heart failure, that have symptoms influenced by posture could alter diagnostic accuracy.**

**KEYWORDS: Diaphragm, myopathy, respiratory muscles**

Sleep-disordered breathing (SDB) has substantial impact on public health [1–4]. Whilst the majority of patients have obstructive sleep apnoea (OSA) [4, 5], other causes of SDB may similarly cause health problems [6–12]. In the present study, we considered the group of patients with neuromuscular disease (NMD) who are affected by SDB because of weakness of the respiratory muscles [9, 13–18] influenced by posture and sleep stage [9, 19] and who do not necessarily present with symptoms, such as daytime fatigue, that are measured by the Epworth Sleepiness scale (ESS) [20].

The gold standard for the detection of ventilatory sleep disorders is polysomnography [21, 22]. However, it is costly and not always immediately available. Therefore, less expensive techniques for domiciliary diagnosis, based predominantly on the registration of flow and detection of respiratory effort, have already been developed to screen for SDB.

The question arises as to whether nocturnal ventilatory problems could be identified by screening questionnaires. The ESS has been validated in patients with OSA [20] and is widely used in sleep laboratories. A comparable tool is not available specifically for patients with NMD. Polysomnography could be selectively offered to those more at risk and treatment, including nocturnal non-invasive ventilation in patients with NMD, could be made available more quickly.

Therefore, we hypothesised that NMD patients with SDB could be identified using a symptom-based questionnaire.

For editorial comments see page 231.

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# Computed tomography assessment of lung volume changes after bronchial valve treatment

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ABSTRACT: **The aim of the present study was to correlate clinical outcome measures following treatment with bronchial valves with regional lung volume. Computed tomography (CT) scan data from 57 subjects with severe emphysema were obtained from nine North American clinical trial sites. IBV® Valves (Spiration, Inc., Redmond, WA, USA) were placed to occlude segmental and subsegmental bronchi in right and left upper lobes using a flexible bronchoscope. Subjects completed a St George's Respiratory Questionnaire (SGRQ), pulmonary function test (PFT) and exercise capacity test. CT scans were analysed at baseline and at 1, 3 or 6 months after treatment to measure total and lobar lung density, volume and mass.**

**Total lung volumes measured using CT were strongly correlated with PFT and did not change with treatment. However, the treated upper lobes significantly decreased in volume in 88% of the observations, by mean±SD 335±444 mL, or a decrease of 10.2% in the 6 month data. The untreated lobes had an 11.6% increase in volume. Changes in regional lung volume were associated with clinically meaningful improvements in SGRQ (-8.95±16.22), but not clinically meaningful PFT changes.**

**The significant health status improvements reported by subjects following bilateral bronchial valve treatment are associated with regional lung volume changes and interlobar shift measured using computed tomography.**

KEYWORDS: **Computed tomography, emphysema, intrabronchial valve, lung volume reduction surgery**

Chronic obstructive pulmonary disease (COPD) is the most common form of primary pulmonary disability [1, 2] and an important cause of mortality when severe. As COPD becomes an end-stage disease, palliative surgical procedures, such as bullectomy for giant bullae, lung volume reduction surgery (LVRS) and lung transplantation, are the only potential treatments remaining.

The National Emphysema Treatment Trial (NETT) and some other smaller studies have shown that, in a selected population of patients with heterogeneous distribution of emphysema and upper-lobe predominance, LVRS can improve patient quality of life, as well as respiratory function, exercise capacity and survival [3–8]. However, surgery in these already high-risk patients has a significant morbidity (20–30%) and a considerable operative mortality (7.9%) within 90 days of the procedure [9].

Therefore, minimally invasive techniques have been proposed as a method to reduce lung volume in these patients without undergoing open thoracotomy [10–15]. One of these new treatments is a one-way valve, which is placed in the segmental bronchi of the most diseased lobes, generally the upper lobes, to prevent air from entering these portions of the lung during normal inspiration while still allowing air to exit. The original hypothesis for this procedure was that the delivery of gas to the treated lobes would be lower than the absorption of gas in these regions resulting in lobar atelectasis, and a reduction of total volume in the diseased lung [11, 12, 15]. This overall reduction in lung volume would result in functional and clinical improvements, similar to those seen with LVRS, but without the invasive surgical procedure. However, several studies have found that the majority of subjects with clinical improvement did not have atelectasis and total lung volume

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# airflow obstruction in an elderly Chinese population

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ABSTRACT: It is common practice to use a forced expiratory volume in one second ($FEV_1$)/ forced vital capacity (FVC) ratio of <70% as evidence of airflow obstruction. As the $FEV_1$/FVC ratio falls with age, the lower limit of normal range (LLN), defined as the bottom 5% in a health reference population, of $FEV_1$ FVC ratio has been suggested as a better index to reduce over-diagnosis of chronic obstructive pulmonary disease (COPD), particularly in the elderly. However, there are no large scale studies that focus on the diagnosis of COPD in the elderly based on these definitions. The present prospective epidemiological study involved 1,149 elderly subjects aged ⩾60 yrs in the community. Detailed questionnaires, pre- and post-bronchodilator spirometry were performed.

In total, 1,008 subjects (mean age 74.2±6.4 yrs; 271 males) completed satisfactory spirometry testing. Airflow obstruction was present in 25.9% as defined by the post-bronchodilator $FEV_1$/FVC ratio of <70% and in 12.4% defined by the LLN of $FEV_1$/FVC ratio. Moderate COPD, at least, was found in 14.0% of patients according to the post-bronchodilator $FEV_1$/FVC ratio of <70% and in 8.5% of patients according to LLN of $FEV_1$/FVC ratio.

In the present elderly Chinese population (mostly females, with low education level and previous exposure to biomass during formative years), the prevalence of chronic obstructive pulmonary disease varied markedly depending on definitions adopted. Further longitudinal studies are needed to determine the precise definition of chronic obstructive pulmonary disease.

KEYWORDS: Airflow obstruction, chronic obstructive lung disease, elderly, lung function

Chronic obstructive pulmonary disease (COPD) was the fifth leading cause of death worldwide in 2001 and it has been predicted by the World Health Organization to rank the third by 2020 [1, 2]. A previous study, based on respiratory symptoms, estimated the prevalence of COPD among the elderly Chinese (aged ⩾70 yrs) living in the Hong Kong as 9% [3]. Objective studies with lung function tests are required for a more accurate estimation of the prevalence of COPD in Hong Kong community.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines currently recommend a fixed spirometric ratio of forced expiratory volume in one second ($FEV_1$)/forced vital capacity (FVC) of <70% for the diagnosis of COPD [4]. However, there are controversies over this simple definition, particularly in the elderly population as the $FEV_1$/FVC ratio falls with age [5–8], therefore, using this definition may result in over-diagnosis of COPD. An alternative way of defining airflow obstruction by is using the lower limit of normal range (LLN) values for the $FEV_1$/FVC ratio, which are based on normal distribution and classify the bottom 5% of the healthy population as abnormal [9, 10]. This approach has been suggested by the GOLD guidelines as one way to minimise the potential misclassification of COPD [4].

There are currently no large-scale studies focusing on the elderly population (aged >60 yrs) that compare the $FEV_1$/FVC fixed ratio of <70% with the LLN of the $FEV_1$/FVC ratio for the assessment of airflow obstruction. The aim of the present study was to assess the prevalence of airflow obstructions in elderly subjects living in the Hong Kong community using these two different definitions. In addition, the agreement of airflow obstructions using the different definitions was compared and their relationships with the symptoms and risk factors of the subjects were assessed.

## METHODS

The present prospective epidemiological study recruited subjects from community centres in

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# Increased airway closure is a determinant of airway hyperresponsiveness

**D.G. Chapman*,#,¶, N. Berend*,#,¶, G.G. King*,#,¶,+ and C.M. Salome*,#,¶**

**ABSTRACT: In order to investigate whether increased airway closure is a component of airway hyperresponsiveness (AHR), airway closure was compared during induced bronchoconstriction in 62 asthmatic, 41 nonasthmatic nonobese (control) and 20 nonasthmatic obese (obese) subjects.**

**Airway closure and airway narrowing were measured by spirometry as percentage change in forced vital capacity (%ΔFVC) and change in forced expiratory ratio (ΔFER), respectively. Multiple regression analyses were used to assess the determinants of AHR, assessed by the dose response slope (DRS).**

**The DRS was significantly increased in asthmatics compared with controls but did not differ between obese and controls. The spirometric predictors of logDRS were baseline FER, ΔFER, body mass index (BMI) and %ΔFVC. There was a negative relationship between BMI and logDRS in the regression, suggesting a protective effect.**

**The present findings suggest that the extent of airway closure during induced bronchoconstriction is a determinant of airway hyperresponsiveness, independent of the level of airway narrowing. However, after adjusting for airway closure, obesity appears to protect against airway hyperresponsiveness.**

**KEYWORDS: Airway hyperresponsiveness, asthma, small airways**

Increased airway closure has been associated with a greater risk of severe asthma exacerbations [1, 2] and with a requirement for oral steroid treatment [3]. Radiological imaging studies have shown that the number of poorly ventilated or nonventilated lung regions correlates with the severity of asthma measured by clinical symptoms and spirometry [1, 4]. These studies suggest that increased airway closure in asthma is an important marker of disease severity. It has recently been proposed that airway hyperresponsiveness (AHR) in sensitised mice can be attributed to an increased susceptibility to small airway closure [2]. However, the role of increased airway closure as a contributing factor to AHR in asthma, defined as an exaggerated and unrestricted response to stimulation of airway smooth muscle, is not known.

It is not clear whether the extent of airway closure differs between asthmatic and nonasthmatic subjects. Using radionuclide imaging, KING *et al.* [5] found no difference in the volume of nonventilated lung measured at residual volume between asthmatic and nonasthmatic subjects. After methacholine-induced bronchoconstriction, airway closure increases in normal subjects [6, 7], but there have been few comparisons of the extent of airway closure during bronchoconstriction between asthmatic and nonasthmatic subjects. MILANESE *et al.* [8] found that airway closure, measured by the relative changes in forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_1$), was similar in asthmatic and rhinitic subjects; however, both these groups had AHR. The mechanical effects of obesity [9–11] may predispose nonasthmatic subjects to increased airway closure during bronchial challenge [12]. If airway closure is an important mechanism for AHR then increased airway closure in obese subjects would be expected to increase responsiveness.

Airway closure is difficult to measure directly but has been estimated indirectly using a range of physiological techniques, such as spirometry [3, 8], nitrogen washout [1, 7] and radionuclide imaging [5, 6]. Using spirometry, airway closure has conventionally been represented by the change in FVC. Previous studies have reported changes in FVC at the provocative concentration of methacholine causing a 20% fall in $FEV_1$ ($PC_{20}$) [3, 13] or concurrent changes in FVC and $FEV_1$ [8] to compare airway closure in subjects with

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