Χρόνιος υγρός βήχας

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Η αιτιολογία του βήχα στα παιδιά περιλαμβάνει ένα ευρύ φάσμα διαταραχών του αναπνευστικού συστήματος και η ανεύρεση της αιτιολογίας είναι απαραίτητη για τη σωστή θεραπευτική αντιμετώπιση. Η συχνότητα με την οποία οι γονείς αναφέρουν τον βήχα ως μεμονωμένο σύμπτωμα, χωρίς την παρουσία κοινού κρυολογήματος, ανέρχεται στο 30% περίπου των παιδιών. Η επικέντρωση της διεθνούς βιβλιογραφίας στο άσθμα τις τελευταίες δεκαετίες είχε ως συνέπεια να υπερτονισθεί η σημασία του βήχα ως συμπτώματος του άσθματος, παρόλο που η διάγνωση του τελευταίου σπανίως τεκμηριώνεται όταν μοναδικό σύμπτωμα είναι ο βήχας.

Στα παιδιά, ο βήχας μπορεί να είναι ιδιαίτερα ενοχλητικός και να έχει σημαντική επίπτωση στον ύπνο, στη σχολική απόδοση, στο παιχνίδι και την άθληση και γενικότερα στην καθημερινότητα τους, αποτελεί δε μια συνεχή πηγή άγχους μέσα στην οικογένεια.

Ορισμοί

Σύμφωνα με την British Thoracic Society, ο βήχας μπορεί να διακριθεί με βάση τη διάρκεια του σε οξύ βήχα που ορίζεται ως πρόσφατης έναρξης με διάρκεια μικρότερη των 3 εβδομάδων και χρόνιο βήχα όταν έχει διάρκεια μεγαλύτερη των 8 εβδομάδων. Ο λόγος που έχει τεθεί το πρώτο όριο είναι γιατί στην πλειονότητα των απλών λοιμωδών αιτίων ο βήχας υποχωρεί το αργότερο μέχρι τις 3-4 εβδομάδες, ενώ το όριο των 8 εβδομάδων προσδιορίζει καλύτερα τα παιδιά που απαιτούν περαιτέρω διερεύνηση. Υπάρχει ωστόσο μια ενδιάμεση χρονική περίοδος μεταξύ των 3-8 εβδομάδων που συνήθως καλείται υποξύς βήχας. Παραδείγματα τέτοιων καταστάσεων είναι ο κοκκύτης και ο μεταλοιμώδης βήχας μετά από ιώσεις του αναπνευστικού. Στην περίπτωση του υποξέος βήχα και εφόσον η ένταση του δείχνει να μειώνεται, είναι προτιμότερο να περιμένουμε μερικές εβδομάδες πριν προχωρήσουμε σε περαιτέρω έλεγχο. Εντούτοις, εάν η ένταση και η συχνότητα του βήχα παραμένουν αμείωτες ή αυξάνονται μετά τις 3 εβδομάδες, ο περαιτέρω διαγνωστικός έλεγχος είναι επιβεβλημένος.

Ως υποτροπιάζων ορίζεται ο βήχας που χαρακτηρίζεται από περισσότερα των δύο επεισοδίων / έτος, διάρκειας τουλάχιστον 7-14 ημερών το καθένα, τα οποία δεν σχετίζονται με τις συνήθεις ιώσεις του αναπνευστικού συστήματος. Εξυπακούεται, πως εάν η διάρκεια των μεσοδιαστημάτων είναι μικρή, η κατηγορία αυτή είναι δύσκολο να διαχωριστεί από τον χρόνιο βήχα.

Χρόνιος υγρός βήχας

Τα παιδιά σπάνια παράγουν πτύελα. Οι βρογχικές τους εκκρίσεις, με τη βοήθεια της βλεννοκροσωτής κάθαρσης και του βήχα, καταλήγουν στον φάρυγγα και στη συνεχεία, μέσω της κατάποσης, στο στομάχι. Κατά συνέπεια, ο όρος “υγρός” (“wet” ή “moist”) βήχας προτιμάται αντί του όρου “παραγωγικός” βήχας που χρησιμοποιείται σε μεγαλύτερα παιδιά και ενήλικες. Η πληροφορία που δίνεται από τους γονείς αναφορικά με την

ποιότητα του βήχα (υγρός ή ξηρός) είναι συνήθως αξιόπιστη και πολύ υποβοηθητική στη διαφορική διάγνωση του συγκεκριμένου συμπτώματος. Ο υγρός βήχας προυποθέτει την παρουσία μεγάλης ποσότητας βλέννης στους αεραγωγούς και όταν είναι χρόνιος υποδηλώνει χρόνια ενδοβρογχική λοίμωξη. Η τελική κατάληξη της χρόνιας ενδοβρογχικής λοίμωξης, εφόσον η εξέλιξη της δεν ανακοπεί έγκαιρα, είναι η βρογχεκτασία.

Η βρογχιεκτασία είναι ένας σαφώς καθορισμένος παθολογοανατομικά όρος, ιδιαίτερα στην ιατρική βιβλιογραφία που αναφέρεται στους ενήλικες. Ορίζεται ως η παρουσία βρόγχων με παχυσμένο, φλεγμονώδες και διατεταμένο τοίχωμα που οφείλεται στην καταστροφή των ελαστικών και μυϊκών δομικών στοιχείων των κατώτερων αεραγωγών. Η κλινική διάγνωση της ωστόσο τίθεται με βάση τα ακτινολογικά ευρήματα της αξονικής τομογραφίας θώρακα υψηλής ευκρίνειας (HRCT), ενώ παλαιότερα χρησιμοποιούνταν η βρογχογραφία. Θα πρέπει να ληφθεί εντούτοις υπόψη πως τα εν χρήσει ακτινολογικά κριτήρια έχουν θεσπιστεί μετά από μελέτες σε ενήλικες και δεν είναι πάντα κατάλληλα για παιδιά. Η γνώση μας για την παθοφυσιολογία της βρογχεκτασίας προέρχεται κυρίως από μελέτες σε άτομα με εγκατεστημένη νόσο που είναι κατά κύριο λόγο ενήλικες όπου σε πολλές περιπτώσεις είναι εμφανές ότι η παθολογική διαδικασία έχει αρχίσει ήδη από την παιδική ηλικία.

Με βάση την κλασική άποψη, η βρογχεκτασία θεωρείται μη αναστρέψιμη. Μελέτες ωστόσο σε παιδιά έχουν δείξει πως η έγκαιρη θεραπευτική παρέμβαση σε ένα πρώιμο «προ-βρογχιεκτατικό» στάδιο μπορεί να σταματήσει ή ακόμη και να αναστρέψει την πορεία της νόσου.

Η βρογχιεκτασία, είναι το τελικό αποτέλεσμα ενός ευρέως φάσματος παθολογικών διεργασιών που προέρχονται από ποικιλία νοσολογικών οντοτήτων, αν και το υποκείμενο αίτιο δεν είναι δυνατό να προσδιορισθεί πάντα. Τα συχνότερα αναφερόμενα στη βιβλιογραφία αίτια είναι η κυστική ίνωση, η πρωτοπαθής δυσκινησία κροσσών, η εισρόφηση ξένου σώματος, η εισρόφηση γαστρικού περιεχομένου, οι υποτροπιάζουσες μικρο-εισροφήσεις σε παιδιά με μείζονα νευρολογικά προβλήματα, οι ανοσοανεπάρκειες και ειδικότερα αυτές που σχετίζονται με διαταραχή της χυμικής ανοσίας, η τραχειο-βρογχο-μαλάκυνση, η αποφρακτική βρογχιολίτιδα και οι μεταλοιμώδεις βλάβες που μπορεί να εγκατασταθούν μετά από πνευμονία, κοκκύτη, ιλαρά και φυματίωση. Σε μελέτη προερχόμενη από δύο παιδοπνευμονολογικά κέντρα αναφοράς από το Ηνωμένο Βασίλειο βρέθηκε πως, εξαιρουμένης της Κυστικής Ίνωσης, το 67% των περιπτώσεων εγκατεστημένης βρογχεκτασίας οφείλονταν σε ανοσοανεπάρκειες, εισροφήσεις και πρωτοπαθή δυσκινησία κροσσών, ενώ στο 25% η νόσος χαρακτηρίστηκε ως ιδιοπαθής.

Με βάση τα όσα προαναφέρθηκαν, η αιτιολογία του χρόνιου υγρού βήχα είναι οτιδήποτε προκαλεί χρόνια ενδοβρογχική φλεγμονή. Τα αίτια όμως της χρόνιας ενδοβρογχικής φλεγμονής δεν διαφέρουν από αυτά της βρογχεκτασίας καθότι, όπως θα δειχθεί και στη συνέχεια του κειμένου, οι καταστάσεις αυτές αντιπροσωπεύουν διάφορα στάδια της ίδιας παθολογικής διαδικασίας. Το μεγαλύτερο μέρος της συζήτησης που ακολουθεί θα αφορά όχι τα γνωστά αίτια που ήδη αναφέρθηκαν αλλά αυτά που χαρακτηρίζονται ως ιδιοπαθή.

Επιδημιολογία των μη οφειλόμενων σε κυστική ίνωση βρογχεκτασιών

Η επίπτωση της βρογχεκτασίας ελαττώθηκε εντυπωσιακά τις δεκαετίες του 1950 και 1960. Το φαινόμενο αυτό αποδόθηκε στην βελτίωση της διατροφής και των συνθηκών υγιεινής, στην εκτεταμένη εφαρμογή εμβολιασμών στα παιδιά ιδιαίτερα κατά του κοκκύτη και της ιλαράς, αλλά κυρίως στην ευρεία χρήση των αντιβιοτικών. Τα επιδημιολογικά δεδομένα που αφορούν στην βρογχεκτασία, και ιδιαίτερα αυτά που αναφέρονται στην παιδική

ηλικία, σπανίζουν. Στην Φινλανδία η συνολική επίπτωση της νόσου εκτιμήθηκε με βάση τις εισαγωγές σε νοσοκομεία κατά την περίοδο 1983-1992, σε 0.039/1000 ανά έτος. Στις ΗΠΑ ο συνολικός επιπολασμός της νόσου εκτιμάται σε 0.52/1000 άτομα. Άλλες μελέτες από τις ΗΠΑ και τη Γερμανία αποτυπώνουν σαφή αύξηση της επίπτωσης της βρογχεκτασίας στους ενήλικες τα τελευταία χρόνια. Μια παρατήρηση ιδιαίτερου ενδιαφέροντος είναι πως παρά την απουσία γνωστών αιτιολογικών παραγόντων στην μεγάλη πλειοψηφία των ενηλίκων ασθενών και τον χαρακτηρισμό της νόσου ως ιδιοπαθούς, υπάρχει ένα σημαντικό ποσοστό ασθενών που αναφέρει έναρξη των συμπτωμάτων (χρόνιου υγρού βήχα) από την παιδική ηλικία.

Παρά το ότι η ακριβής επίπτωση της βρογχεκτασίας στα παιδιά παραμένει άγνωστη, ή νόσος έχει πάψει πλέον να θεωρείται σπάνια. Είναι αρκετά συχνή σε πληθυσμούς με χαμηλό επίπεδο διαβίωσης, όπως σε παιδιά ιθαγενών πληθυσμών της Αλάσκας και της Κεντρικής Αυστραλίας (ετήσιες επιπτώσεις: 16/1000 και 15/1000, αντίστοιχα). Τα παιδιά από Δυτικές χώρες έχουν μικρότερο κίνδυνο ανάπτυξης βρογχεκτασιών. Σε μελέτη από τη Βόρεια Αγγλία, η αδρή εκτίμηση του επιπολασμού της βρογχεκτασίας στα παιδιά <17 ετών ανήλθε σε 0,172/1000. Στην ίδια μελέτη φάνηκε ότι η μέση ηλικία εκδήλωσης συμπτωμάτων και της διάγνωσης μέσω της αξονικής τομογραφίας ήταν τα 1,1 έτη και τα 7,2 έτη, αντίστοιχα. Στη Φινλανδία η επίπτωση ανέρχεται σε 0,005/1000 ενώ στην Νέα Ζηλανδία υπάρχει μεγάλη διακύμανση μεταξύ των εθνικών ομάδων της χώρας που κυμαίνεται μεταξύ 0,015 και 0,178/1000. Στην τελευταία αυτή μελέτη διαπιστώθηκε πως η επίπτωση ήταν 3 και 12 φορές μεγαλύτερη στους Μαορί και στους Πολυνήσιους, αντίστοιχα, σε σχέση με τα παιδιά ευρωπαϊκής καταγωγής. Παρόλο που οι παραπάνω αριθμοί μόνο πολύ αδρά μπορούν να αποτυπώσουν τη συχνότητα με την οποία απαντάται η νόσος, η σύγκριση τους καθιστά φανερό ότι η παιδική βρογχεκτασία απαντάται κυρίως σε χαμηλού κοινωνικο-οικονομικού επιπέδου πληθυσμούς.

Παθοφυσιολογία της βρογχεκτασίας και των σχετιζόμενων με αυτή νοσολογικών οντοτήτων

Κεντρική θέση στην παθογένεση της νόσου κατέχει η διαταραχή της βλεννοκροσσωτής κάθαρσης. Το έναυσμα για την έναρξη της παθολογικής διεργασίας είναι συνήθως η προσβολή από έναν λοιμώδη παράγοντα (συνήθως ιό) που βλάπτει τον βλεννοκροσσωτό μηχανισμό καθιστώντας τον λιγότερο λειτουργικό. Αποτέλεσμα αυτού είναι ο αποικισμός των κατώτερων αεραγωγών με βακτήρια του ανώτερου αναπνευστικού που κινητοποιούν φλεγμονώδεις αντιδράσεις. Οι τελευταίες με τη σειρά τους οδηγούν σε επιδείνωση της βλάβης των κροσσών και ουσιαστικά, επέρχεται αδυναμία κάθαρσης των βακτηρίων. Το τελικό αποτέλεσμα είναι η εγκατάσταση των βακτηρίων υπό μορφή βιομεμβρανών και η χρόνια βακτηριακή φλεγμονή των βρόγχων. Το βρογχικό τοίχωμα προοδευτικά καταστρέφεται από τις τοξίνες των βακτηρίων και τους μεσολαβητές της φλεγμονής. Ο παραπάνω παθογενετικός μηχανισμός που χαρακτηρίζεται ως «φαύλος κύκλος» περιγράφηκε αρχικά από τον Cole το 1986 και θεωρείται πως περιγράφει επαρκώς την ανάπτυξη της βρογχεκτασίας.

Εάν οι αρχικές βλάβες αφεθούν να εξελιχτούν, με την πάροδο του χρόνου θα γίνουν εμφανείς οι χαρακτηριστικές της βρογχεκτασίας στην HRCT. Δεδομένου ότι η αρχική φάση της διαδικασίας που οδηγεί στην εμφάνιση των ακτινολογικών ευρημάτων είναι άγνωστη, η διάγνωση μπορεί να διαφύγει σε έναν αριθμό παιδιών που έχουν συμπτώματα συμβατά με βρογχεκτασία χωρίς όμως σαφή ακτινολογική εικόνα. Ο όρος “χρόνια πυώδης πνευμονική νόσος” (“chronic suppurative lung disease”) χρησιμοποιείται για την περιγραφή της νοσολογικής οντότητας με κλινική συμπτωματολογία παρόμοια με της βρογχεκτασίας αλλά με απουσία των χαρακτηριστικών ακτινολογικών ευρημάτων στη HRCT. Η κύρια

συμπτωματολογία σε αμφότερες τις καταστάσεις είναι η παρατεταμένη διάρκεια του υγρού βήχα. Μια παρόμοια κατάσταση, η οποία αναφέρεται στη βιβλιογραφία ως “χρόνια εμμένουσα βρογχίτιδα” (“protracted bacterial bronchitis”), ορίζεται ως η μεμονωμένη παρουσία χρόνιου υγρού βήχα (>4 εβδομάδες) με ανταπόκριση στην αντιβιοτική αγωγή, με παράλληλη απουσία εναλλακτικών διαγνώσεων. Οι τρεις αυτές καταστάσεις – βρογχεκτασία, χρόνια πυώδης πνευμονική νόσος και χρόνια εμμένουσα βρογχίτιδα – δεν αποτελούν διαφορετικές οντότητες αλλά αντιπροσωπεύουν το ευρύ φάσμα της ενδοβρογχικής λοίμωξης, η οποία εάν αφεθεί χωρίς θεραπεία θα προχωρήσει από τη χρόνια εμμένουσα βρογχίτιδα στη χρόνια πυώδης πνευμονική νόσο και τελικά στην ακτινολογικά εμφανή βρογχεκτασία.

Συμπτωματολογία βρογχεκτασίας και προ-βρογχιεκτασικών καταστάσεων

Το κεντρικό σύμπτωμα της βρογχεκτασίας και των προ-βρογχιεκτασικών καταστάσεων είναι ο βήχας που είναι πάντα χρόνιος και υγρός. Ο υγρός χαρακτήρας υποδηλώνει την παρουσία υπερβολικής ποσότητας εκκρίσεων στους βρόγχους. Τα μεγαλύτερα παιδιά μπορούν να παράγουν πτύελα, ωστόσο αυτό είναι κάτι που σπάνια απαντάται στις μικρότερες ηλικίες. Ο ξηρός χαρακτήρας του βήχα ωστόσο δεν μπορεί να αποκλείσει την παρουσία μικρότερης ποσότητας εκκρίσεων. Με την πρόοδο όμως της παθολογικής διεργασίας ο βήχας θα αποκτήσει τελικά υγρό χαρακτήρα. Τα περισσότερα παιδιά είναι προσχολικής ηλικίας αν και η έναρξη του νοσήματος μπορεί να συμβεί από τη βρεφική ηλικία έως την ενήλικο ζωή. Στην πλειονότητα των περιπτώσεων η ακρόαση των πνευμόνων είναι φυσιολογική.

Μερικές φορές το ιστορικό που δίνουν οι γονείς είναι συμβατό με αυτό του άσθματος, και περιλαμβάνει δύσπνοια κατά την άσκηση, συριγμό, νυχτερινό βήχα και εξάρσεις με τις λοιμώξεις του ανώτερου αναπνευστικού. Στις περιπτώσεις αυτές χρειάζεται αρκετή προσοχή και επιμονή στη λήψη των λεπτομερειών το ιστορικού για να διευκρινισθεί η ακριβής φύση των συμπτωμάτων. Ένα από τα συνηθέστερα λάθη είναι να αντιλαμβάνονται οι γονείς ως συριγμό τον ήχο που παράγεται από την μετακίνηση των εκκρίσεων στους μεγάλους βρόγχους ο οποίος στην διεθνή βιβλιογραφία αποδίδεται ως «rattle». Υπάρχει βέβαια πάντα και η περίπτωση ο συριγμός μπορεί να υπάρχει πραγματικά, δεδομένου ότι το άσθμα μπορεί να συνυπάρχει και μάλιστα να αποτελεί και προδιαθεσικό παράγοντα για την ανάπτυξη χρόνιας ενδοβρογχικής λοίμωξης. Κατά την άσκηση μπορεί να προκαλείται έντονος βήχας που να εμποδίζει το παιδί να ολοκληρώσει τη δραστηριότητα του. Αυτό γίνεται συχνά αντιληπτό από τους γονείς ως δύσπνοια κατά την κόπωση παρόλο που η πραγματική δύσπνοια απουσιάζει. Ως πληροφορία όμως μπορεί να στρέψει τον παιδίατρο προς την κατεύθυνση του άσθματος. Οι ιογενείς λοιμώξεις του αναπνευστικού αποτελούν το συνηθέστερο αίτιο εξάρσεων του άσθματος αλλά και της χρόνιας ενδοβρογχικής λοίμωξης. Στην ενδοβρογχική λοίμωξη τα βακτήρια σχηματίζουν βιομεμβράνες μέσα στις οποίες επιβιώνουν με πολύ χαμηλό μεταβολισμό και πολλαπλασιάζονται με πολύ αργό ρυθμό. Είναι γνωστό πως η είσοδος ιών στις βιομεμβράνες επιταχύνει δραματικά τον μεταβολισμό και τον πολλαπλασιασμό τους με αποτέλεσμα να έχουμε επέκταση της βιομεμβράνης. Αυτό παράγει μια αρκετά έντονη συμπτωματολογία με επιδείνωση του υγρού βήχα χωρίς όμως κατά κανόνα να υπάρχει δύσπνοια. Επειδή υπάρχουν πολλές αναλογίες με τα ασθματικά παιδιά που εμφανίζουν εξάρσεις της νόσου τους κατά τη διάρκεια ιογενών λοιμώξεων, είναι εύκολο η διάγνωση να οδηγηθεί προς την κατεύθυνση του άσθματος και να αφεθεί έτσι χρόνος στην ενδοβρογχική λοίμωξη για να επεκταθεί.

Διαγνωστική προσέγγιση

Η διάγνωση της χρόνιας εμμένουσας βρογχίτιδας τίθεται κλινικά. Ωστόσο, αρχικά θα πρέπει να αποκλειστούν οι σπανιότερες αλλά κατά κανόνα σοβαρές καταστάσεις, που επίσης εκδηλώνονται με υγρό βήχα. Έτσι, είναι σκόπιμο, λαμβάνοντας πάντα υπόψη την κλινική εικόνα και το ιστορικό, να διενεργηθεί δοκιμασία ιδρώτα ή/και μοριακός γενετικός έλεγχος για κυστική ίνωση, ανοσολογικός έλεγχος (ανοσοσφαιρίνες, υποτάξεις IgG, απάντηση σε πολυσακχαριδικά και πρωτεϊνικά αντιγόνα), έλεγχος για πρωτοπαθή δυσκινησία κροσσών (ρινικό μονοξείδιο του αζώτου, έλεγχος κινητικότητας κροσσών και έλεγχος δομής κροσσών σε ηλεκτρονικό μικροσκόπιο), έλεγχος για γαστρο-οισοφαγική παλινδρόμηση, διαταραχές κατάποσης και εισροφήσεις.

Ο προσδιορισμός των υπεύθυνων παθογόνων μικροοργανισμών είναι πολύ σημαντικός γιατί θα μας καθοδηγήσει στη θεραπεία, δεν είναι όμως καθόλου εύκολος. Η παραγωγή πτυέλων στα παιδιά είναι, όπως προαναφέρθηκε, πολύ δύσκολη και γι αυτό συνήθως αρκούμαστε στη λήψη επιχρισμάτων από τον οπίσθιο φάρυγγα μετά τη διενέργεια φυσιοθεραπείας και την πρόκληση βήχα (cough swabs). Η ευαισθησία και ειδικότητα ωστόσο των συγκεκριμένων καλλιεργειών είναι φτωχή. Τα συνηθέστερα υπεύθυνα βακτήρια είναι ο μη τυποποιήσιμος H. influenza, ο Streptococcus pneumoniae, η Moraxella catarrhalis, η Pseudomonas aeruginosa και ο Staphylococcus aureus.

Στην απλή ακτινογραφία θώρακα τα ευρήματα θα ελλείπουν ή θα είναι φτωχά και ασαφή. Εξαίρεση αποτελούν παιδιά με προχωρημένη νόσο όπου μπορεί να απεικονίζονται περιοχές ατελεκτασίας ή να υπάρχουν ευρήματα συμβατά με βρογχεκτασίες.

Η εύκαμπτη βρογχοσκόπηση και η αξονική τομογραφία υψηλής ευκρίνειας HRCT είναι τα δύο κύρια διαγνωστικά εργαλεία για την εκτίμηση της μορφολογίας των αεραγωγών και την έκταση των βλαβών στα παιδιά με χρόνιο υγρό βήχα. Η HRCT μπορεί να ανιχνεύσει διάταση των αεραγωγών αλλά στα αρχικά στάδια της νόσου στερείται ευαισθησίας και το μόνο που συνήθως καταδεικνύει είναι πάχυνση των βρόγχων, η εκτίμηση της οποίας όμως ενέχει υψηλό βαθμό υποκειμενικότητας. Η εύκαμπτη βρογχοσκόπηση σαφώς υπερέχει της HRCT ως προς την ποσότητα και ποιότητα των πληροφοριών που παρέχει ενώ επιπλέον μέσω της λήψης βρογχοκυψελιδικού εκκρίματος (BAL) δίνεται η δυνατότητα καλλιέργειας υλικού απευθείας από τους βρόγχους. Ωστόσο, η βρογχοσκόπηση, παρόλο που δεν συνοδεύεται από κίνδυνο σοβαρών επιπλοκών, δεν παύει να είναι επεμβατική μέθοδος. Επιπλέον, δεν παρέχει εικόνα για την κατάσταση των μικρότερων περιφερικών βρόγχων. Γενικά, οι δύο αυτές μέθοδοι θεωρούνται ότι παρέχουν συμπληρωματικές πληροφορίες και συχνά είναι αναγκαίο να πραγματοποιηθούν και οι δύο.

Θεραπεία

Αντιβιοτικά

Τα αντιβιοτικά είναι η βάση της θεραπείας για παιδιά με όλο το φάσμα των οντοτήτων που αρχίζει από την εμμένουσα βακτηριακή βρογχίτιδα και φτάνει στην βρογχεκτασία. Ο τρόπος χορήγησης τους ποικίλλει ανάλογα με την κάθε περίπτωση και μπορεί να είναι από του στόματος, ενδοφλέβια ή μέσω εισπνοών με νεφελοποίηση. Η χρήση τους ωστόσο είναι σε μεγάλο βαθμό εμπειρική δεδομένου ότι δεν υπάρχουν σαφώς τεκμηριωμένες μελέτες σε παιδιά. Τα δοσολογικά σχήματα και η διάρκεια της αγωγής διαφέρουν σημαντικά από κέντρο σε κέντρο. Προτιμώνται αντιβιοτικά ευρέως φάσματος που να καλύπτουν για τα συνηθέστερα από τα υπεύθυνα βακτήρια (H. influenzae, S. pneumoniae, and M. catarrhalis) ή η επιλογή στηρίζεται στα αποτελέσματα των καλλιεργειών πτυέλων ή BAL, εφόσον βέβαια σε αυτές έχουν απομονωθεί βακτήρια. Το κυριότερο κριτήριο πάντως είναι η αποτελεσματικότητα του κάθε φορά χορηγούμενου αντιβιοτικού που καθορίζεται από την

κλινική πορεία του κάθε ασθενή ξεχωριστά. Ανεξάρτητα από το είδος του αντιβιοτικού και το δοσολογικό σχήμα που θα επιλεγεί, η διάρκεια της θεραπείας είναι παρατεταμένη. Σε ορισμένες ανθεκτικές περιπτώσεις μπορεί να επιβάλλεται ακόμη και η συνεχής χορήγηση αντιβιοτικών σε θεραπευτικής δόσης για αρκετούς μήνες. Σε περίπτωση απομόνωσης Ps. aeruginosa ακολουθούνται τα θεραπευτικά πρωτόκολλα της κυστικής ίνωσης.

Φυσιοθεραπεία

Οι διάφορες τεχνικές φυσιοθεραπείας των πνευμόνων συμβάλλουν σε μεγάλο βαθμό στη βελτίωση της βλεννοκροσσωτής κάθαρσης και αποτελούν αναπόσπαστο τμήμα της θεραπευτικής αντιμετώπισης των παιδιών αυτών. Ανεξάρτητα από την τεχνική που θα επιλεγεί, η φυσιοθεραπεία θα πρέπει να γίνεται συχνά (δύο φορές την ημέρα με διάρκεια τουλάχιστον 15-20 min κάθε φορά). Η τεχνική διδάσκεται στον ασθενή ή στους οικείους του και εφαρμόζεται στο σπίτι από τον/τους ίδιους. Είναι απαραίτητη ωστόσο η τακτική επαφή των ασθενών με τους υπεύθυνους φυσιοθεραπευτές (ανά 1-3 μήνες) έτσι ώστε να γίνεται διόρθωση των λαθών κατά την εφαρμογή της τεχνικής καθώς και για να γίνεται αναπροσαρμογή της μεθόδου ανάλογα με την ικανότητα, την ηλικία, και την κλινική πορεία του ασθενούς. Συχνά, πριν από κάθε συνεδρία φυσιοθεραπείας χορηγούνται εισπνοές υπέρτονου διαλύματος NaCl που ρευστοποιούν τις εκκρίσεις καθιστώντας ευκολότερη την αποβολή τους.

Αντιασθματικά

Η χρήση τους δικαιολογείται σε παιδιά με ιστορικό συριγμού ή συμπτωματολογία ενδεικτική άσθματος. Παρόλο που δεν συμβάλλουν άμεσα στην αντιμετώπιση των νοσημάτων του φάσματος της χρόνιας ενδοβρογχικής λοίμωξης, ο έλεγχος του άσθματος, εφόσον αυτό υπάρχει, είναι κεφαλαιώδους σημασίας στην αντιμετώπιση της μικροβιακής ενδοβροχικής φλεγμονής, δεδομένου ότι το άσθμα μπορεί να δράσει συνεργικά ευοδώνοντας την εγκατάσταση και ανάπτυξη των βακτηρίων.

Συμπεράσματα

Είναι σαφές πως υπάρχουν ακόμη πολλά αναπάντητα ερωτήματα σχετικά με την παθογένεση του φάσματος των νοσολογικών οντοτήτων στο οποίο περιλαμβάνονται η εμμένουσα βακτηριακή βρογχίτιδα, η χρόνια πυώδης πνευμονική νόσος και η βρογχεκτασία. Η αδυναμία πλήρους κατανόησης του παθογενετικού μηχανισμού που αφορά στην εξέλιξη αλλά κυρίως στην εγκατάσταση της νόσου, αντανακλά και στην ασάφεια και την έλλειψη βιβλιογραφικών δεδομένων όσον αφορά στη θεραπευτική προσέγγιση των νοσημάτων αυτών. Ωστόσο, από τον συνεχώς αυξανόμενο αριθμό παιδιών που προσέρχονται στα παιδοπνευμονολογικά τμήματα πάσχοντας από αυτά τα νοσήματα, και παρά την απουσία τεκμηριωμένων επιδημιολογικών μελετών, είναι σαφές πως αποτελούν πλέον ένα σημαντικό πρόβλημα υγείας του παιδικού πληθυσμού. Η διαγνωστική τεκμηρίωση των νοσημάτων αυτών είναι σχετικά πολύπλοκη ωστόσο η υποψία τους τίθεται σχετικά εύκολα με την παρουσία χρόνιου υγρού βήχα. Ο τελευταίος θα πρέπει να πάψει να θεωρείται πάντα ως συνέπεια άσθματος και να αντιμετωπίζεται με αντιασθματική αγωγή. Η παραπάνω λανθασμένη τακτική θα έχει ως συνέπεια την απώλεια πολύτιμου χρόνου που θα δώσει τη δυνατότητα επέκτασης της ενδοβρογχικής φλεγμονής, καθιστώντας ακόμη δυσκολότερη την αντιμετώπιση της.

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CME article

Chronic cough in children

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EDUCATIONAL AIMS

- To provide a framework for the approach to children with chronic coughing who don't already have a specific disorder.
- To review the causes and management of children with chronic non-specific dry coughing.
- To review the causes and management of children with chronic wet cough.
- To define and review 'protracted bacterial bronchitis'.

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SUMMARY

Chronic cough has been variably defined as a cough lasting longer than 3, 4 or 8 weeks. Many post viral or pertussis like illnesses are associated with prolonged coughing that resolves over time. Management involves first trying to make a diagnosis and identify the presence of any underlying condition. Targeted treatments can then be employed. Trials of treatments are often used to make a diagnosis. Because natural resolution of cough is so common any trial of treatment to confirm a diagnosis should be time limited and the treatment only restarted if the coughing returns. Only a small proportion of children with an isolated non-specific dry cough have asthma and care is needed not to over diagnose asthma. Children with chronic wet cough may have protracted bacterial bronchitis (PBB) that responds to a full course of antibiotics. Children with PBB failing to respond to treatment or with specific pointers should be investigated for specific causes of suppurative lung disease.

INTRODUCTION

Chronic cough is one of the most common symptoms that parents will present with their children to the physician. Coughing is often distressing and impacts on the child's ability to sleep well, play and attend school. There is often a discrepancy between what parents and paediatricians consider to be normal. In addition, the reporting of cough is not always accurate and may depend on how parents or school teachers are affected by the child's coughing. The underlying diagnosis in chronic cough can remain elusive and for many there are no specific or effective treatments available. It is therefore often a frustrating consultation for both paediatricians and parents. Most respiratory disorders can present with coughing and the list of causes of chronic cough is large. Several national and international guidelines on the management of cough in children have been published.[1,2]

Cough is one of the most important airway protective reflexes which is under both voluntary and involuntary control. Cough receptors which sense and respond to changes in temperature, chemicals and mechanical stresses are located in the pharynx, larynx and tracheobronchial tree. When stimulated these receptors send signals back to the cough centre in the medulla oblongata which then triggers the easily recognizable sequence of events that constitute a cough. A deep inspiration precedes closure of the glottis with a subsequent forceful contraction of the respiratory muscles, the glottis then opens, and there is a forceful expulsion of air, mucous and potentially any other foreign body. During the initial deep inspiration children can inhale any foodstuff that is in the pharynx or larynx exacerbating any choking or coughing. The mechanism of the cough obviously depends on intact receptors, nerves, a functioning cough centre and sufficiently strong expiratory and laryngeal muscles. The cough reflex is lost when consciousness in significantly impaired. Centrally acting cough

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suppressants are therefore ineffectual because of the degree of sedation required to produce cough suppression.

Normal children cough on average 11 times per day when they are well with the coughing increasing in frequency and severity during the frequent winter URTIs.[3]

In general there are a few overlapping reasons underlying why children appear to have problem chronic cough:

- they are repetitively trying to prevent pulmonary aspiration
- they have chronic airways irritation and inflammation
- they have chronic airways mucus hypersecretion
- they have some extra respiratory cause of the cough

Given that coughing is an important protective reflex it isn't logical to try to suppress coughing without first identifying and treating the underlying reason.

Definition of chronic cough

One in ten otherwise normal children with acute cough due to an upper respiratory tract infection (URTI) are still coughing 3 weeks later.[4] Many of these children have what has been labeled a 'post infectious cough' (prolonged acute coughing after an obvious URTI) perhaps due to a pertussis, mycoplasma or other viral infection.[5,6] Some children have a tendency to develop cough receptor hypersensitivity (CRH) following each viral URTI (recurrent prolonged acute coughing) and this state of CRH can last many weeks to months (Figure 1).[7,8]

Defining chronic cough as lasting longer than 8 weeks is therefore preferable to using a shorter duration e.g. 3–4 weeks. Eight weeks was used in the British Thoracic Society Guideline Recommendations for the assessment and management of cough in children (1). Providing that the child is otherwise well, waiting for and checking that natural resolution has occurred is reasonable. However this duration of a chronic cough is defined largely on the basis of epidemiology rather than pathology. A cough of shorter duration can be highly significant in neonates or in older children with other 'red flag' symptoms. A wait and see policy should not be undertaken if 'red flag' alerts are present (Box 1).

It is unclear whether children with frequently recurrent cough in the absence of URTI should be assessed and managed any differently from children with true chronic coughing. Brooke et al.[9] investigated the long term outcome of 125 pre-school children with recurrent cough. Over time more than 50% had outgrown the coughing, but only 10% had started to wheeze. The remainder of children who continued to have recurrent cough showed an increased prevalence of nocturnal coughing and decreased threshold to inhaled methacholine. Interestingly, nearly 17% of the control children were nocturnal coughers.[9]

CLINICAL APPROACH

In the history the characteristics of the cough should be carefully elicited (Box 2). There are certain characteristic cough types which are readily recognized including:

Pertussis or whooping cough which is characterized by severe paroxysms of coughing. In this, a spasm or paroxysm of coughing is followed by a gasping inspiration producing the characteristic whoop. The characteristic whoop of pertussis may not be heard in very young infants or older aged children and adolescents.[10,11]

A loud or brassy cough may be characteristic of tracheomalacia, and particularly when associated with tracheoesophageal fistula (a 'ToF cough').

Psychogenic coughs may appear like 1] dry repetitive habit 'tic-like' coughs or 2] bizarre and honking with the child not being very disturbed by the cough. Both coughs usually disappear when the child is engrossed in an activity or asleep.

Most doctors and parents will also differentiate between a wet and dry cough. Often parents will use terminology which is less clear such as 'a chesty cough' or a 'smoker's cough'. Children under 5 years rarely spit out phlegm but rather swallow it. A chronic productive or wet cough suggests some underlying cause for mucous hypersecretion that needs investigated whereas a dry cough suggests airway irritation, inflammation or a non- airways cause of the cough. It is important to note that some children with dry coughing will have periods with a wet cough e.g. with respiratory infections.

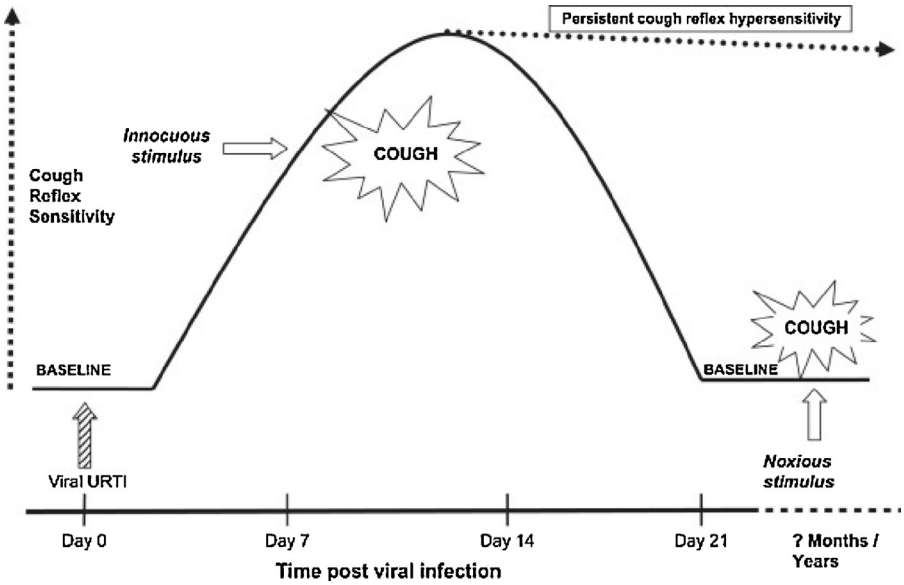

Figure 1. Schematic of proposed changes in cough reflex sensitivity following viral upper respiratory tract infection. (reprinted with permission from L. McGarvey *et al.*, Pulmonary Pharmacology & Therapeutics 2009; 22: 59-64).

Box 1. List of some red flag symptoms and signs in chronic cough.

- Coughing started suddenly with a choking episode or an inhaled foreign body is suspected
- Coughing is relentlessly progressive
- There are already specific pointers for an underlying diagnosis including
  - Weight loss, night sweats suggestive of TB
  - Haemoptysis
  - Signs of chronic lung disease or ill-health already present (poor growth, finger clubbing, chest wall abnormality and abnormal lung sounds)
- Coughing with a background history of recurrent pneumonia
- Cough starting in neonatal period
- Swallowing difficulties
  - With craniofacial abnormality
  - With neuromuscular disorder
- Dyspnoea – chronic or exertional
- Wet cough lasting more than 3-4 weeks

Box 2. A list of some key questions to ask in the history.

1. How and when the cough started?
2. Is the cough an isolated symptom?
3. What triggers the cough?
4. Does the cough disappear when the child goes to sleep?
5. What is the nature and quality of the cough?
6. What treatments has the child been tried on and how beneficial were they?
7. What other medication is used? e.g. ACE inhibitors
8. Is there a family history of respiratory, allergic or infectious disease?
9. Does the child smoke? Do the parents smoke? Is there evidence of any environmental pollutant at home?
10. How disruptive is the cough?
11. Is there evidence of Obstructive Sleep Apnoea? How large are the tonsils?

Physical Examination

It is important to do a full clinical examination. General inspection including assessment of growth may reveal evidence of failure to thrive, or clues to atopic status (eczema, allergic salute of Allergic Rhinitis). Low muscle tone particularly in infants may be associated with feeding difficulties and specific neuromuscular conditions with respiratory sequelae. Similarly, craniofacial and palatal abnormalities can be associated with swallowing dysfunction. Examination of the nose and throat may reveal evidence of rhinitis or post-nasal drip or very rarely problems with dentition associated with acid GOR. Check the auditory meatus as wax in the external auditory meatus can be associated with chronic cough via stimulation of the Arnold's nerve reflex. Some respiratory signs should prompt full investigations including finger clubbing, chest deformity, abnormal breath sounds or reduced or asymmetrical air entry. Abnormalities in other systems particularly the cardiovascular system may point to a particular diagnosis. Enlargement of lymph glands, liver or spleen should lead to investigations of possible chest masses or TB.

It is worth trying to observe the child's cough. In children who are old enough to cough on request, both the sound of the cough and the presence of palpable airway secretion should be assessed. This can easily be done in younger children by placing one hand on the anterior and the other hand on the posterior chest.

INVESTIGATION

Most children with problem chronic coughing will require investigations or a diagnostic trial of specific therapy.

- Infants and especially those who cough or become chesty during or after a feed, should have their feeding observed by a trained nurse or speech and language therapist.
- With the help of a physiotherapist obtain a sample of sputum. The sample can be studied for bacteria, atypical organisms and viruses. Some centres are able to perform a differential cell count on an induced sputum sample. An elevated percentage eosinophils (>3%) is supportive evidence for asthma and the presence of bacteria associated with neutrophilia is in keeping with a bacterial infection such as protracted bacterial bronchitis.
- A chest radiograph will give a good overview of the state of the lungs and may give indications for further investigations. A chest radiograph may not be indicated if a mild specific disorder is definitively diagnosed (e.g. asthma / allergic rhinitis or if a pertussis-like illness is clearly resolving). However, a normal chest radiograph does not always exclude significant pathology such as bronchiectasis and further imaging may be needed.
- Spirometry and bronchodilator responsiveness. In children over 5 years this gives a good overview of the current state of the airway calibre and whether they widen with bronchodilator.
- Allergy testing – skin prick testing or IgE specific tests when positive put the cough into a background of atopy and make cough variant asthma a possible diagnosis.

AETIOLOGY OF CHRONIC COUGH

Several attempts have been made to extensively investigate cohorts of children with chronic cough who have been referred to specialist centres and are summarised in Table 1.[10–12]

Marchant et al reported that the common causes of chronic cough in children in an Australian setting differed from those commonly reported in adults (asthma, GORD, upper airways syndrome). They found that protracted bacterial bronchitis (defined later) was the commonest cause (40%). Natural resolution occurred during the period while investigations were being undertaken in 22%. Asthma, gastro-oesophageal reflux disease (GORD) and upper airways cough syndrome (UACS) collectively accounted for only 10%. However, two other studies, one from the USA and the second from Turkey, reported higher percentages of children with asthma, GORD and UACS (Table 1).[13–15]

The differences in the common causes found may be related to 1] different durations for the definition of chronic cough, 2] different local disease prevalence, 3] different referral practices from primary care, 4] different ages of children studied and 5] different uses of 'trials of treatment' and some aspects of selective investigations. Given that natural resolution of chronic cough in children is common the use, timing and order of 'trials of treatment' could have a profound effect on the final diagnosis arrived upon. It is likely that very young children, as in the Australian study, differ most from adults.

Table 1
Summary findings from three studies comprehensively investigating children with chronic cough.

Study	Marchant JM et al Chest 2006; 129(5): 1132-1141	Khoshoo V et al Chest 2009; 136: 811-815	Asilsoy S et al Chest 2008; 134: 1122-1128
Country	Australia	USA	Turkey
Number	108 children referred to tertiary respiratory centre	40 children referred to pulmonary clinic	108 children referred to Children's Hospital & Research Centre
Average age of child when studied (years)	Median 2.6 years	Mean 7.8 years	Mean 8.4 years
Definition of chronic cough (greater than)	3 weeks	8 weeks	4 weeks
Average length of coughing at referral	Median 6 months	18 weeks	4.16 months
Evaluations undertaken	CXR, FEV1, ENT assessment, bronchoscopy/BAL Sweat test, IgGs, allergy tests, HRCT, pH studies, mycoplasma/pertussis tests	CXR, FEV1, ENT assessment, bronchoscopy/BAL Sweat test, IgGs, allergy tests, HRCT, pH studies, mycoplasma/pertussis tests	CXR, FEV1, ENT assessment, bronchoscopy/BAL, IgGs, allergy tests, HRCT, gastroesophageal scintigraphy, mycoplasma/pertussis tests
Final diagnosis	PBB – 40% Natural Resolution – 22% Bronchiectasis – 6% Asthma – 4% UACS – 3% GORD – 3% Habit – 1%	GORD – 27% UACS – 23% Asthma – 13% Infection – 5% Aspiration – 2% Multiple aetiologies – 20% All tests normal – 10% (? habitual cough)	Asthma – 25% PBB – 23% UACS – 20% PBB + asthma – 12% UACS + asthma - 7% GORD – 5% Bronchiectasis – 3% Natural resolution 2% Others – TB, mycoplasma

It is difficult to know how representative these studies are for chronic cough in the community given the relative low prevalence of post viral syndromes and pertussis detected. These contrast with the community based study of a large number of children coughing greater than 2 weeks more than one third of whom tested positive for a recent pertussis illness. Natural resolution of the cough occurred in almost all the children. The median duration of cough was 118 days in the pertussis positive group, 39 days in mycoplasma positive group and 70 days if neither positive (likely postviral cough).[5,6]

This suggests that and pertussis, postviral and mycoplasma illnesses are common causes of prolonged coughing in the community especially in older children. Recent reports from the USA and Australia have confirmed an increase in older children and adolescents with pertussis.[8,13,16]

It clearly is not ethically correct (other than in a research setting) to subject all children to a full battery of potentially invasive tests for conditions that experience shows is likely low probability.

There is currently a clinical trial testing the added value of a chronic cough management pathway compared with usually practice underway in several centres in Australia.[17] In the meantime, the presence or absence of pointers suggesting specific and serious lung disease will determine the requirements for more detailed investigations.

SPECIFIC CAUSES AND MANAGEMENT OF CHRONIC COUGH

Otherwise healthy child with chronic dry or recurrent cough

The term 'non-specific isolated chronic dry cough' is used for an otherwise well child for whom no specific diagnosis can be arrived at. They truly have increased coughing and this collective term likely includes children with a range of conditions such as:

1. *Post-infectious cough or pertussis*. About one third of children older than 5 years with prolonged acute coughing have pertussis with the median duration of cough approaching 4 months.[2] The paroxysmal spasms of cough followed by an inspiratory whoop typically seen in young children may not be seen in very young infants or older children. Others have Mycoplasma or a respiratory viral infection eg rhinovirus or RSV.[5,6,18] In the vast majority the cough resolves naturally with time. It is important to confirm cough resolution. It is likely that these children are experiencing a slow recovery of their airway mucosal epithelial cells and during this time they have cough receptor hypersensitivity (Figure 1). Anti-asthma therapy does not seem to be beneficial.
2. *Cough variant asthma.* Some children with asthma have coughing as the predominant feature and wheezing has not been heard by a health professional. A trial of anti-asthma therapy (inhaled corticosteroids, ICS) may be required especially if there are other atopic diseases (eczema, allergic rhinitis). Trials of asthma therapy should be effectively delivered, given over a limited time frame and have objective end points. At the end of the trial the asthma medication should be stopped. A negative response suggests the coughing is unresponsive to ICS and asthma unlikely. A positive response may indicate natural resolution of the cough or cough variant asthma. If coughing recurs then the medication can be restarted. A second positive response is suggestive of cough variant asthma.
3. *Allergic Rhinitis and/or post nasal drip (upper airways syndrome)*. This is not accepted by all as a common cause of true chronic coughing in children. Children with allergic or perennial rhinitis undoubtedly have a clearing the throat type snorting cough. True coughing may be due to associated allergic airways inflammation (asthma). Cough due to allergic rhinitis should respond to allergen exclusion where possible and intranasal steroids with or without antihistamines.
4. *Psychogenic coughs*. There appears to be 2 types of psychogenic cough. Firstly, children may develop a dry repetitive 'tic-like' cough after an episode of bronchitis. This type of cough is usually not very disruptive and parents often can identify that the cough has become a habit. Other children develop bizarre honking coughs which, by being very disruptive to school and family life, bring some secondary gain for the child. Typically these coughs do not upset the children (la belle indifference), the coughing reduces when the child is engrossed in some activity and when asleep. Biofeedback, distraction and suggestion psychotherapies may be required.
5. Other potential causes include;
   a. Wax in the external ear canal has been associated with chronic coughing.
   b. Hypertrophied tonsillar tissue impinging on the epiglottis.

c. Gastro esophageal reflux (GOR) is a major cause of chronic coughing in adults and responds to a long course of proton pump inhibitors. It has been much more difficult to show GOR to be the cause in children and evidence including multichannel intraluminal impedance and pH monitoring associating GORD and cough in children has been reviewed and is conflicting.[19–21] While empirical treatment helps GOR symptoms it seems to do little for the respiratory symptoms. However, anecdotally most physicians have encountered children who have persistent cough with perhaps other symptoms of gastro-oesophageal reflux whose cough responds magically to antireflux therapy and in selected children a trial of antireflux therapy can be useful.
d. Children started on ACE inhibitors may have a problem dry cough which stops once the ACE inhibitor is stopped. However, children with cardiac problems can also cough because of associated airway problems, pulmonary odema, Kartagener's syndrome or immunodeficiency.
e. Children's Interstitial Lung disease (child) usually presents with breathlessness but early evolving cases can be associated with a dry repetitive cough

6. Chronic non-specific isolated dry cough is a label used when there are no pointers to a specific diagnosis.

Productive (moist or wet) cough

A chronic cough that sounds wet or productive implies either an increase in airway secretions or abnormalities in clearance. Children with persistent productive (moist or wet) cough should be investigated to determine if they have any of the specific suppurative lung conditions with persistent endobronchial infections that eventually may lead to bronchiectasis such as those listed in Box 3.

Persistent bacterial bronchitis (PBB) seems to be a common and increasingly recognised cause of chronic wet cough in young children and often occurs on a background of mild asthma or has been misdiagnosed as asthma.[22] Seear et al.[23] reintroduced the term paediatric chronic bronchitis to describe a cohort of children with chronic productive cough that didn't fit any other major diagnostic category. Some of the children reported had previously had invasive medical therapy (prolonged ventilation, cardiac surgery) and many came from poor socioeconomic backgrounds with an over representation of native American Indians.[23] Further reports from Chang AB (Australia) and Everard M (Sheffield, UK) highlighted the existence of this condition which has now largely been accepted.[22–24,28] These children have chronic wet productive coughing, with bacteria such as Pneumococcus, Haemophilus influenza, and Moraxella persisting in the airways and if a broncoalveolar lavage or sputum is obtained there is an associated neutrophilia. Spirometry in older children is usually normal (but the child may cough during the procedure) and the CXR typically is normal or has non-specific bronchial wall thickening. The cough responds to a full or prolonged course of antibiotic (eg co-amoxiclav, for 2–4 weeks). These authors speculated that either an early respiratory insult (e.g. infectious or medically induced) has led to chronic self-perpetuating inflammation with the formation of bacterial biofilms that can be difficult to treat. Douras et al.[25] evaluated 93 selected children with wet cough lasting >6 weeks who did not have asthma and reported that the duration of cough and intensity of BAL neutrophil count related to worse HRCT scan scores. In addition, they noted that some children were referred late for evaluation (wet coughing for > 12 months) and, like Chang et al., speculated that the emphasis of 'asthma under diagnosis' in the last 2 decades of asthma literature may have contributed to a misdiagnosis of children with chronic cough.[22] Recently, Kompare and Weinberger[26] have reported a large series of children with protracted bacterial bronchitis which mostly had started in infancy.[26] Almost three quarters of the children had an associated airway malacia (tracheal, bronchial). These children responded well to antibiotics, although a significant number relapsed and needed further courses of antibiotics.

Box 3. List of major conditions associated with chronic wet coughing.

- Persistent bacterial bronchitis
- Cystic Fibrosis
- Immune deficiencies
- Primary ciliary disorders
- Recurrent pulmonary aspiration
- Retained inhaled foreign body

A positive response to a full course of an appropriate antibiotic and the child returning to completely good health confirms the diagnosis of PBB and further investigations will likely be unnecessary.

However, if PBB fails to respond or is PBB becomes recurrent further investigations are required to rule out the other conditions listed above. It is quite possible, although as yet unproven, that each episode of recurrent bacterial bronchitis is triggered by a viral infection and we currently only recommend a second 2 week course of antibiotic should this recurrence of wet productive cough last longer than 3 weeks. It is important to establish the presence of an underlying diagnosis to allow disease specific therapy to be instituted. This includes a sweat test and genotyping (cystic fibrosis), nasal nitric oxide, cilial ultrastructure and beat frequency (Primary Ciliary Dyskinesia), white cell count, immunoglobulins and functional antibody studies (lung infections associated with immune deficiencies), barium swallow, swallowing videofluorscopy and 24 pH studies (recurrent pulmonary aspiration).

An HRCT is useful to define the extent of lung disease and to confirm the presence of bronchiectasis. A bronchoscopy may also be required to rule out a retained foreign body and to obtain lung samples for microbiology.

It is still uncertain as to whether PBB is a fore runner to bronchiectasis or adult COPD.

Chronic brassy barking or seal-like cough

This cough suggests a tracheal or glottic cause eg tracheo- and / or bronchomalacia. Many children who have undergone tracheooesophageal fistula (TOF) surgery have tracheomalacia and develop a loud cough ("TOF – cough") which is especially disruptive during an intercurrent infection.

Relentlessly progressive coughing

A cough that is progressively becoming more severe and violent needs investigated early. Causes, apart from pertussis, include an expanding intrathoracic tumour, a retained inhaled foreign body and TB.

Haemoptysis

Chronic cough with haemoptysis requires investigation and may be due to cystic fibrosis or other bronchiectasis, retained inhaled foreign body, tumour, pulmonary haemosiderosis or artiovenous malformation.

There are many other rare causes for chronic coughing in children including the dry cough associated with the children's Interstitial Lung Diseases (child).

MANAGEMENT

The management of cough relies on firstly making the correct diagnosis and then managing the underlying condition. Treatment of the symptom of cough in isolation is usually unsatisfactory. Many cough suppressants are no more than soothing preparations for the throat. Cough suppressants such as opioids which are effective usually produce significant sedation if used in the dose required for cough suppression. There is little evidence of benefit in chronic cough without a clear underlying diagnosis. It is important to:

- Remove the child from environmental tobacco smoke or other pollutant exposure.
- Try to make a specific diagnosis and use specific treatments (find and use the relevant up to date guideline).

Non-specific isolated cough in an otherwise well child

A recent overview of Cochrane Library reviews on the treatment of chronic non-specific cough in children concluded that there was little evidence to recommend anti-histamines, inhaled corticosteroids (ICS), beta 2 agonists, leukotriene receptor antagonists or gastro-oesophageal reflux treatments. Very high dose ICS may have some benefit but the benefits are likely outweighed but the side effects.[27] However, because most of these coughs resolve naturally over time a positive response does not confirm the diagnosis. Trials of these therapies need to be time-limited and retried.[28]

Chronic wet cough

Chronic wet cough is a specific pointer to a potentially more serious lung condition. Protracted bacterial bronchitis seems to be the most common cause and almost by definition responds well to antibiotics. The overview of Cochrane Library reviews on the treatment of chronic wet cough in children concluded that antibiotic therapy was reasonable first step but warned that the children should be reevaluated to ensure cough resolution.[27]

RESEARCH DIRECTIONS

- The role of recurrent viral bronchitis as a cause of chronic cough
  - What would be the benefits of rapid viral, pertussis and mycoplasma diagnosis in reducing unnecessary investigations and reassuring parents?
  - Do children with recurrent problem coughing have the same factors and diagnoses as those with chronic persistent cough?
  - Are there any predictors for response to trials of ICS (eg Exhaled Nitric Oxide) ?
- The natural history of protracted bacterial bronchitis – how often is it a pre-bronchiectasis condition?
- What is the best treatment of **recurrent** protracted bacterial bronchitis?
- Why does protracted bacterial bronchitis occur? Is there an immune deficiency?
- What are the indications and best method for investigations into GORD as a cause of chronic cough?

CONFLICT OF INTEREST

MD Shields – nil immediately relevant to this review. MD Shields has received honoraria (from Glaxo Smith Kline, AstraZeneca, Novartis, Merck Sharp Dohme) for talks given at educational meetings. He has received sponsorship from the same companies to attend the ERS, EAACI and BTS annual educational meetings.

GM Doherty– nil immediately relevant to this review. GM Doherty has received honoraria (Novartis) for talks given at educational meetings. He has received sponsorship from Glaxo-Smith Kline to attend the ERS annual educational meetings.

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CME SECTION

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CME QUESTIONS

MCQs

1. A two year old boy presents with a twelve week history of wet-sounding cough. His parents report no other symptoms. On physical examination there is an intermittent palpable 'rattle' over the upper chest. Initial investigations should include:
a. Spirometry
b. Bronchoalveolar lavage
c. High-resolution computed tomography of the chest
d. Chest radiograph
e. All of the above
2. The following is true of gastroesophageal reflux
a. It is known to be a frequent cause of cough in children
b. It can be associated with severe suppurative lung disease
c. Fundoplication should be considered in isolated persistent cough which fails to respond to maximal medical anti-reflux therapy
d. An elevated lipid-laden macrophage index is a specific indicator of chronic cough secondary to reflux
e. A similar proportion of adults and children with cough have GORD
3. Chronic cough secondary to pertussis
a. Is unlikely in the absence of the characteristic inspiratory 'whoop'.
b. Responds well to an appropriate course of macrolide antibiotics
c. Should be treated with high-dose systemic steroids
d. May occur in fully vaccinated young children
e. Occurs in around 5% of children over the age of five with a cough of more than two weeks
4. Cough-variant asthma
a. Is more common than wheeze-variant asthma
b. Requires treatment with inhaled corticosteroids for more than six months before effects can be seen
c. Will usually present with a wet-sounding cough
d. Frequently responds to inhaled bronchodilators
e. Is more common in children with a personal history of atopy
5. Normal children
a. Usually cough more than 30 times per day
b. Have a 10% chance of cough persisting for more than 3 weeks after an URTI
c. Generate increased intrathoracic pressure against an open glottis at the start of a cough
d. Cough more frequently during REM sleep
e. All of the above

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ORIGINAL ARTICLE

Asthma and protracted bronchitis: Who fares better during an acute respiratory infection?

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Aim: Acute respiratory infections (ARI) are common in children, and symptoms range from days to weeks. The aim of this study was to determine if children with asthma have more severe ARI episodes compared with children with protracted bronchitis and controls.

Methods: Parents prospectively scored their child's next ARI using the Canadian acute respiratory illness and flu scale (CARIFS) and a validated cough diary (on days 1–7, 10 and 14 of illness). Children were age- and season-matched.

Results: On days 10 and 14 of illness, children with protracted bronchitis had significantly higher median CARIFS when compared with children with asthma and healthy controls. On day 14, the median CARIFS were: asthma = 4.1 (interquartile range (IQR) 4.0), protracted bronchitis = 19.6 (IQR 25.8) and controls = 4.1 (IQR 5.25). The median cough score was significantly different between groups on days 1, 7, 10 and 14 ($P < 0.001$). A significantly higher proportion of children with protracted bronchitis (63%) were still coughing at day 14 in comparison with children with asthma (24%) and healthy controls (26%).

Conclusion: Children with protracted bronchitis had the most severe ARI symptoms and higher percentage of respiratory morbidity at day 14 in comparison with children with asthma and healthy controls.

Key words: asthma; children; cough; morbidity; respiratory tract infection.

Acute respiratory infections (ARI) are common in children, varying from four episodes per year in the first 2 years of life to two to three episodes per year when aged 2 to 5 years.[1] The morbidity of ARI in children includes cough and non-specific symptoms such as irritability.[2] Among individuals, these symptoms vary in severity and length of illness.[1] Cough related to ARI generally resolves between 1 and 3 weeks in most children.[3,4] Although health practitioners often view ARIs as a benign self-limiting illness, parental concerns regarding the length and severity of their children's symptoms and illness often lead to presentation to their family doctor.[1,5] Furthermore, to ameliorate the symptoms of ARIs, 'over-the-counter' cold and cough medications are often used.[6] Indeed 'over-the-counter' cough and cold medications cost the community billions of dollars each year despite the lack of evidence on their efficacy.[7]

Key Points

1. Children with protracted bronchitis have more severe acute respiratory infections (ARI) in comparison to children with asthma and healthy controls.
2. A higher proportion of children with protracted bronchitis still cough after day 14 of ARI in comparison to children with asthma and healty controls.
3. Cough scores in children with asthma and healthy controls are similar on day 7 and day 14 of ARI.

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In children with asthma, ARIs often lead to acute exacerbations of asthma.[8] Acute asthma exacerbations in children are a common presentation to emergency departments and are a substantial economic burden on the health-care system.[9] Additionally, it places a burden on the children, their parents and families, and is associated with a decrease in their quality of life.[10,11] Yet, there are no studies (PubMed search – May 2007) that have examined the severity or length of ARI symptoms in children with acute asthma.

Children with some conditions such as tracheomalacia and protracted bronchitis have prolonged coughing[12] illnesses. Cough is the most common symptom presenting to doctors in the USA[13] and Australia, and one of the most common symptoms of ARIs. Protracted bronchitis is a recently described entity[14] that has probably been recognised but not well described until recently.[15] It is clinically defined as: (i) the presence of isolated chronic moist cough; (ii) resolution of cough with appropriate antibiotics; (iii) absence of pointers suggestive of alternative specific cough [12]; and (iv) positive bronchoalveolar lavage culture (growth of $>10^4$ colony forming units/mL).[14] One likely contributing factor to protracted bronchitis is innate immunity dysfunction.[16] Whether children with protracted bronchitis have more severe ARI symptoms are however unknown.

Measurement of the severity of ARI symptoms is however limited as there are few validated instruments. One validated instrument is the Canadian acute respiratory illness and flu scale (CARIFS)[17] which has been utilised in several settings.[18] Another validated instrument is that for the symptom of cough,[19] a common symptom of ARIs.

The aim of our study was to determine if children with asthma or protracted bronchitis have more severe ARI symptoms at presentation and at days 7, 10 and 14 using validated scales (CARIFS and cough score)[17,19] compared withcontrols. We also examined (using a validated cough score[19]) if children with asthma or protracted bronchitis were more likely to have a persistent cough on day 14 than controls. We hypothesised that children with asthma have more severe and/or prolonged ARI symptoms than the other two groups.

Methods and Materials

Subjects

Three groups of children were recruited: children with asthma ($n = 72$), children with protracted bronchitis ($n = 19$) and healthy controls ($n = 23$). The two first groups were primarily from other studies. Children with asthma were recruited from an emergency department during an acute exacerbation of asthma. Asthma was defined as recurrent (>2) episodes of wheeze and/or dyspnoea with a clinical response (decreased respiratory rate and work of breathing) to $beta_2$ agonist. An asthma exacerbation was defined as acute deterioration of asthma control requiring treatment with more than a single dose (>600 ug via metered dose inhaler and spacer or >2.5 mg nebuliser) of salbutamol in an hour. The children with asthma were prescribed either 3 or 5 days of oral prednisone and no difference was found between the groups, as also described by others.[20] Parents of children with protracted bronchitis (as defined earlier) were from another study.[14] The parents were approached during an outpatient's visit. The parents were asked to document their next ARI episode for 2 weeks; and the children did not receive any antibiotics during that period. Each child with protracted bronchitis had undergone a bronchoscopy to determine if any airway lesion was present. Children were excluded if tracheomalacia or bronchomalacia was present.[21] A series of investigations was also undertaken in these children to exclude an underlying cause of their chronic cough, such as cystic fibrosis, mycoplasma infection or an underlying major immune problem.[14] Controls were recruited from a convenient sample of family and friends; they had no history of smoking or presence of asthma. The parents were asked to document the next ARI episode once their child had 24 h of runny nose, cough, sore throat and/or fever. Exclusion criteria were children with neuro-developmental dysfunction, cardiorespiratory illnesses (e.g. cystic fibrosis or tracheomalacia) or children with any type of immunodeficiency. Written informed consent was obtained and the studies were approved by our institution's ethics committee.

Protocol

All parents completed two types of daily diary cards (CARIFS[17] and cough[19]) for the first 7 days and on days 10 and 14 of illness at enrolment (for asthma group) or during the next episode when their child was unwell with an ARI (for the protracted bronchitis group and controls). The parents of children with protracted bronchitis and controls were asked to start filling out the diary cards after their child had been sick for at least 24 h with symptoms of cough, runny nose, sore throat and/or fever. The protracted bronchitis group and controls were age- and season-matched for the asthma group (winter period = April to September; summer period = October to March). Reminders were sent to the latter two groups on a monthly basis.

CARIFS

CARIFS (Appendix I) was 'developed as a parentally assessed disease severity measure appropriate for ARI, including influenza, in children'.[18] The scale consists of 18 items that included measurements of symptoms (e.g. cough), function (e.g. play) and parental impact (e.g. clinginess).[17] Each item has a 4-point ordinal score; 'Major Problem' = 3, 'Moderate Problem' = 2, 'Minor Problem' = 1 and 'No Problem' = 0. In addition, items could also be scored as 'Don't know or Not Applicable'. Each set of parents completed diary cards for the morning (AM) and evening (PM). The final daily accumulated score is derived from the addition of all the scores, divided by the total number of questions answered, multiplied by 36 (the total number of questions that could have been answered for both AM and PM).

Cough diary

The validated cough diary utilised was one that included a measure of impact.[19] The child's cough was scored as follows: 0 = no cough; 1 = cough for one or two short periods only; 2 = cough for more than two short periods; 3 = frequent coughing but does not interfere with school or other activities; 4 = frequent coughing which interferes with school or other activities; and 5 = cannot perform most usual activities because of severe coughing.

Statistical analysis

The children were categorised into three groups: asthma, protracted bronchitis or healthy controls. Non-parametric analysis was used as the data were not normally distributed. Kruskal–Wallis or Mann–Whitney test was used for three and two group comparisons, respectively. Chi-square was used to compare categorical variables. Spearman's correlation coefficient (r_s) was used to examine the correlation between variables. SPSS version 13 (SPSS Inc., Chicago, IL, USA) was used for all statistical calculations. A two-tailed P-value of ≤ 0.05 was considered significant.

Results

The demographics (age, gender, season of ARI) of the children enrolled were matched (Table 1). The median age (interquartile range (IQR)) of the combined group was 3.8 years (3.8), with 64 boys and 50 girls. The median age (IQR) of the three groups of children was: asthma = 3.8 years (3.8), protracted bronchitis = 3.3 years (3.9) and controls = 3.9 years (3.4), $P = 0.49$. Of the 72

Table 1 Demographics of study participants divided into children with asthma, protracted bronchitis and healthy controls

	Asthma group $n = 72$	Protracted bronchitis $n = 19$	Controls $n = 23$
Median age (IQR)	3.8 (3.8)	3.3 (3.9)	3.9 (3.4)
Sex			
Male (%)	39 (54.2)	12 (63.2)	14 (60.9)
Female (%)	33 (45.8)	7 (36.8)	9 (39.1)
Season			
Winter (%)	43 (59.7)	11 (57.9)	10 (43.5)
Summer (%)	29 (40.3)	8 (42.1)	13 (56.5)

IQR, interquartile range.

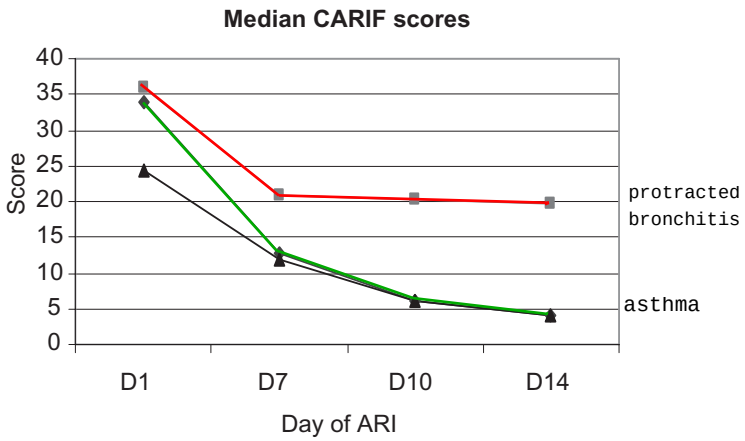

Fig. 1 Daily median Canadian acute respiratory illness and flu scale (CARIFS) as reported by the parents of children with asthma (◆), protracted bronchitis (■) and healthy controls (▲) on days 1, 7, 10 and 14 of acute respiratory infection (ARI).

children with asthma, 39 were male and 33 were female. In the group of 19 children with protracted bronchitis, 12 were male and seven were female. The healthy control group had 14 males and nine females. There was no significant difference in gender among the groups ($P = 0.87$). There was also no significant difference between the seasons when dividing the year into two seasons: winter period (April to September) and summer period (October to March). Sixty-five of the illnesses began in the season of April–September and 49 between October and March. In the winter period, 43 ARIs were from children with asthma, 11 from protracted bronchitis group and 10 from healthy controls. In the summer season, the numbers were 29, 8 and 13 ARIs, respectively. There was no significant difference among the the groups ($P = 0.391$) in relation to the seasons.

On day 1 of the ARI there was no difference between the median-accumulated CARIFS score, $P = 0.168$. The median CARIFS scores were: group with asthma = 34 (IQR 34.8), group with protracted bronchitis = 36 (IQR 36.6) and controls = 24.4 (28.0) (Fig. 1). However, children with protracted bronchitis had a significantly higher median CARIFS score than children with asthma and controls on days 10 and 14 of illness, $P < 0.001$ and $P < 0.001$, respectively. On day 14, the median CARIFS scores were: asthma = 4.1 (IQR 4.0), protracted bronchitis = 19.6 (IQR 25.8) and controls = 4.1 (IQR 5.25) (Fig. 1).

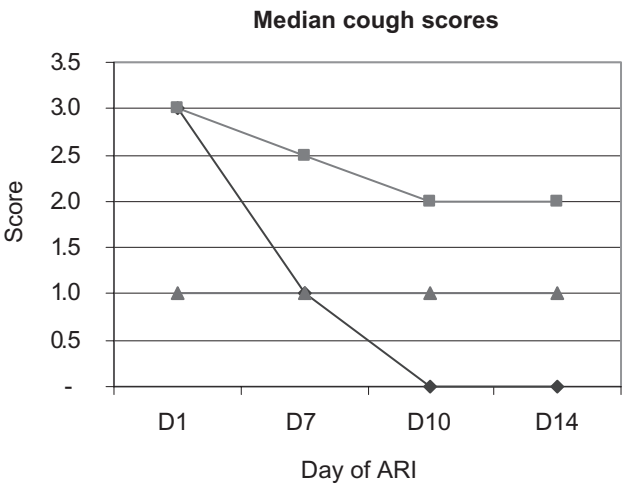

Fig. 2 Median cough scores of children with asthma (◆), protracted bronchitis (■) and healthy controls (▲) against the days of acute respiratory infection (ARI) (days 1, 7, 10 and 14).

Cough scores

On day 1, median cough scores were significantly different between groups ($P < 0.001$); median (IQR) in the group with asthma was 3.0 (1.45), protracted bronchitis = 3.0 (2.0) and healthy controls = 1.0 (1.0). The median scores were also significantly different between groups on days 7, 10 and 14. By day 14 the median cough scores (IQR) were: asthma group = 0 (1.0), protracted bronchitis group = 2.0 (2.0) and healthy controls group = 1.0 (1.25) (Fig. 2).

When those with asthma were compared with those with protracted bronchitis, the groups were similar on day 1 ($P = 0.83$) but the asthma group had a significantly lower score on days 7, 10 and 14 of ARI ($P<0.001$ for all). Similarly, healthy controls did not significantly differ from children with protracted bronchitis on day 1 ($P = 0.08$) but differed significantly on days 7, 10 and 14, $P = 0.03$, $P = 0.02$ and $P = 0.02$, respectively. The scores in children with asthma and the healthy controls were similar on day 7 ($P = 0.56$), day 10 ($P = 0.21$) and day14 ($P = 0.5$) but significantly differed on day 1 ($P < 0.001$) (Table 2).

When evaluated by proportions, there was a significant difference between the groups, with children with protracted bronchitis having had the highest proportion of still coughing on days 7, 10 and 14 (Table 3). The proportion of children with asthma who were coughing were significantly higher than controls on day 1 ($P < 0.001$) but similar with controls on days 7, 10 and 14 ($P = 0.56$, 0.21 and 0.05, respectively). Cough scores significantly related to CARIFS scores on all days (day 1, $r_s = 0.574$, $P < 0.001$; day 7, $r_s = 0.477$, $P = <0.001$; day 10, $r_s = 0.639$, $P < 0.001$; and day 14, $r_s = 0.499$, $P < 0.001$).

Table 2 Median cough score and interquartile range (IQR) of three groups on days 1, 7, 10 and 14

Children with:	Day 1		Day 7		Day 10		Day 14	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Asthma	3.0	1.45	1.0	1.0	0	1.0	0	1.0
Protacted bronchitis	3.0	2.0	2.5	1.25	2.0	2.0	2.0	2.0
Controls	1.0	1.0	1.0	2.75	1.0	2.0	1.0	1.25

Table 3 Proportion of children with asthma, protracted bronchitis and healthy controls coughing at days 1, 7, 10 and 14 of acute respiratory infection (ARI) as per cough diary[19]

Children with	Day 1		Day 7		Day 10		Day 14	
	n	%	*n*	%	*n*	%	*n*	%
Asthma	49	68	31	43	20	28	14	24
Protacted bronchitis	12	63	13	68	14	74	12	63
Controls	8	35	7	30	6	26	6	26
P-value*	<0.001		<0.001		<0.001		<0.001	

**P* by Kruskal–Wallis comparing the three different groups on a particular day of ARI.

Discussion

This is the first study to compare the severity of ARIs as measured by CARIFS and cough scores in children with asthma, protracted bronchitis and healthy children. We have demonstrated that children with asthma had more severe scores than controls in the early phase of the asthma exacerbation but not in the later phase (day 10 onwards). In contrast, children with protracted bronchitis had the most severe scores, and 63% were still coughing by day 14.

Despite the commonality of ARIs, there is relatively little data on the impact and effect of ARIs in children. In the validation phase of CARIFS, Jacob *et al.*[17] reported that by day 14, 80% of their study subjects had a CARIFS score of less than 3. Butler *et al.*[22] stated that <7% of their 240 subjects were still unwell at day 14 as scored using CARIFS. Both these studies were of children who were presenting to their general practitioner with ARI, that is, they were children from the community and thus likely to be otherwise well children. Our data on healthy controls were similar with their data as we found that the controls had day 14 CARIFS scores of 4.1. However, we could not find any study on (PubMed search 29 May 2007) using CARIFS on children with asthma. Thus, this study is unique as we examined if children with asthma have more severe ARI episodes at presentation and at days 7, 10 and 14 using validated scales (CARIFS and cough score). Authors have described that children with asthma are likely to have more ARIs[9] and, thus, it is biologically possible that children with asthma also have more severe ARIs. However, we found that on subjective scoring using CARIFS, parents of children with asthma reported similar profiles with controls on day 10 onwards. Using the CARIFS, children with asthma had a higher score only on day 7, but by day 10, had a similar score with controls. The cough diary scores of children with asthma were higher than controls on day 1 but not on other days. The differences found between the two scales are not surprising as the scales utilised were designed to measure different things. Furthermore, it is known that the severity of cough has a poor relationship to the severity of asthma.[23,24]

In our study, children with protracted bronchitis had the highest CARIFS score on days 7, 10 and 14, and this was significantly higher than children with asthma or healthy controls. Protracted bronchitis is a condition characterised by isolated chronic (>4 weeks) wet cough that responds to antibiotics.[14] One possible reason why the severity of ARI is higher in this group is the presence of dysfunction of the innate immunity such as reduced expression of toll-like receptors 2 and 4 in the airway cells.[16] The clinical implications of this finding are two-fold. First, doctors may choose to use these data to advise parents of children with protracted bronchitis that their child is likely to have another episode of ARI which is subjectively more severe than otherwise well children. Second, the study also highlights the importance of the diagnosis of protracted bronchitis and its possible relationship to chronic suppurative lung disease.[25]

Another possible reason is that the subjective reporting, as our results have, has to be interpreted with the knowledge that parental reporting of childhood respiratory symptoms can be biased and parental perceptions are likely to play an important role.[26] However, as young children are unable to verbally express themselves adequately, it is standard practice for parents to be proxy assessors of their young child. Moreover, the burden of illness is real, and Juniper has shown that physicians are poor assessors of the burden of illness.[27] Nevertheless, biased reporting, as the reason why children of different groups have significant different scores, is unlikely, as we have previously shown the number of coughs objectively recorded on a cough metre per subjective-score unit in diaries completed by parents of children with chronic cough was significantly higher than that of coughs recorded in diaries completed by parents of otherwise well children.[28] This suggests that parents of children with chronic cough are unlikely to exaggerate the severity of their child's cough. Also, Wyke and colleagues had shown that the higher severity of cough in socio-economically deprived children was real and not because of parental exaggeration.[29]

Our study was also limited by the small sample size in the controls. A larger sample size in the protracted bronchitis group and healthy controls would have been beneficial. In addition to the limited sample size, this study looked at one episode of illness only and was limited to a 14-day period. A further limitation was that we do not have polymerase chain reaction data for viral

detection on these children. Also, the children with asthma were recruited during an exacerbation and received oral corticosteroids, and thus, the children we described were 'treated asthmatics'. However, we found that the respiratory morbidity of children who received 3 days of oral corticosteroids was similar to those who received 5 days of corticosteroids.[30] Family history or personal history of atopy was not reported in any of our groups. It may be possible but remains unknown whether children with atopy have more prolonged respiratory symptoms. Given these limitations, our study's findings should be confirmed in other cohorts and include a longer follow-up phase.

In conclusion, children with protracted bronchitis had the most severe ARI symptoms and higher percentage of respiratory morbidity at day 14. In comparison with controls, children with asthma had more severe ARI symptoms only in the early phase (at, and before, 7 days). As protracted bronchitis is an important and common cause of chronic cough in children[21] and possibly antecedent to chronic lung disease, further research studies to ascertain the natural history and mechanisms underlying protracted bronchitis[31,32] are important.

Appendix I

Canadian acute respiratory illness and flu scale[17] as completed by parents of children with asthma, protracted bronchitis and healthy controls

	Major problem	Moderate problem	Minor problem	No Problem	Do not know/Not applicable
Fever					
Cough					
Poor appetite					
Not sleeping well					
Irritable					
Feels unwell					
Low energy, tired					
Not playing well					
Crying more than usual					
Needing extra care					
Clinginess					
Nasal congestion, runny nose					
Vomiting					
Not interested in what is going on					
Unable to get out of bed					
Headache					
Sore throat					
Muscle aches and pains					

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Bacterial Distribution in the Lungs of Children with Protracted Bacterial Bronchitis

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Abstract

Objectives: Flexible bronchoscopy with bronchoalveolar lavage (FB-BAL) is increasingly used for the microbiological confirmation of protracted bacterial bronchitis (PBB) in children with a chronic wet cough. At our centre, when performing FB-BAL for microbiological diagnosis we sample 6 lobes (including lingula) as this is known to increase the rate of culture positive procedures in children with cystic fibrosis. We investigated if this is also the case in children with PBB.

Methods: We undertook a retrospective case note review of 50 children investigated for suspected PBB between May 2011 and November 2013.

Results: The median (IQR) age at bronchoscopy was 2.9 (1.7–4.4) years and the median (IQR) duration of cough was 11 (8.0–14) months. Positive cultures were obtained from 41/50 (82%) and 16 (39%) of these patients isolated ≥2 organisms. The commonest organisms isolated were *Haemophilus influenzae* (25 patients), *Moraxella catarrhalis* (14 patients), *Staphylococcus aureus* (11 patients) and *Streptococcus pneumoniae* (8 patients). If only one lobe had been sampled (as per the European Respiratory Society guidance) 17 different organisms would have been missed in 15 patients, 8 of whom would have had no organism cultured at all. The FB-BAL culture results led to an antibiotic other than co-amoxiclav being prescribed in 17/41 (41%) patients.

Conclusions: Bacterial distribution in the lungs of children with PBB is heterogeneous and organisms may therefore be missed if only one lobe is sampled at FB-BAL. Positive FB-BAL results are useful in children with PBB and can influence treatment.

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Introduction

Chronic cough is a common symptom in children and a frequent reason for specialist referral. [1,2] Although underlying lung disease must always be excluded, the majority of children with chronic cough have otherwise normal lungs. Protracted bacterial bronchitis (PBB), describes chronic infection of the conducting airways and is characterised by an antibiotic-responsive, wet cough persisting for longer than 4 weeks. [3] Increasing numbers of children are being diagnosed with PBB but it is unclear if this is due to a true increase in incidence or increased recognition. [4] It has been proposed that the incidence of PBB may have been affected by physicians prescribing fewer courses of antibiotics for lower respiratory tract infections that are presumed to be viral [5,6].

Microbiological confirmation of PBB poses a significant challenge as affected children rarely expectorate sputum. As a result, PBB has the potential to be missed, misdiagnosed or inadequately treated. This can potentially lead to structural damage of the respiratory system and increase the chance of symptoms persisting. [7] The gold standard method of sampling the lower airways in young children is flexible bronchoscopy with bronchoalveloar lavage (FB-BAL). This is safe and has a low rate of complications. [8] At our centre, children with suspected PBB who have not responded to a 2 week course of oral antibiotics are investigated with a chest x-ray (CXR) and FB-BAL. Those with positive BAL cultures are then treated with a 6 week course of an appropriate oral antibiotic. Other centres choose to treat patients with a prolonged course of antibiotics prior to gaining a microbiological diagnosis, reserving FB-BAL for children who do not respond or relapse.

When undertaking FB-BAL in children with suspected PBB, it is our practice to perform single aliquot bronchial washings from each of the 6 lobes (including the lingula). This differs from the European Respiratory Society (ERS) guidance which recommends a triple aliquot sample from a single lobe. [9] Our practice is based on the knowledge that this methodology is safe and has been used to demonstrate a heterogeneous distribution of bacteria in the

Table 1. FB-BAL results from the 15 patients in whom positive cultures would have been missed if the right middle lobe had been sampled alone.

	RUL	RML	RLL	LUL	Lingula	LLL
1	HI, MC			HI		
2		HI, MC	HI, MC	HI, MC	HI, MC, SP	HI, MC, SP
3	HI, MC, SP	HI, MC, SP	HI, MC, SA	HI, MC, SP	HI, MC, SP	HI, MC, SP
4						HI
5			SA	SA	SA	SA
6	HI, MC, CA	HI, CA	HI, CA	HI, MC, CA	HI, CA	HI
7				SA		SA
8	SA	HI, SA	HI, SA, HP	HI, SA		SA
9						MC
10		HI, SP	HI, SP, SA	HI	HI, SP	HI, SP
11						GNB
12				MC	MC	MC
13						HI
14		HP	HI		HI	HI
15	MC, SP	MC	SA		SA	MC

RUL: right upper lobe, RML: right middle lobe, RLL: right lower lobe, LUL: left upper lobe, LLL: left lower lobe, CA: *Candida albicans,* GNB: Gram-negative bacillus, HI: *Haemophilus influenza,* HP: *Haemophilus parainfluenzae,* MC: *Moraxella catarrhalis,* SA, *Staphylococcal aureus*; SP, *Streptococcus pneumoniae.*
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lungs of children with other respiratory conditions, such as cystic fibrosis (CF). [10] The aim of this study was to review the FB-BAL and CXR results in children with PBB, to assess the bacterial distribution across lung lobes in children with PBB.

Methods

We retrospectively reviewed the case notes of 50 consecutive children investigated for suspected PBB between May 2011 and November 2013 at the University Hospital of North Staffordshire. As defined by the Health Research Authority guidance this project was service evaluation, patient consent was therefore not obtained. All patient information was anonymised and de-identified prior to analysis. All the FB-BAL procedures had all been performed under general anaesthesia and patients had been requested not to take any antibiotics in the preceding 7 days. The procedure was identical in all patients. The bronchoscope (2.8 mm BF-XP260F or 4.0 mm BF-P260F; Olympus America Inc, Center Valley, USA) was introduced to the lower airway via a laryngeal mask, and the suction port not used until the tip of the bronchoscope was below the level of the carina. Single aliquot bronchial washings were obtained from each lobe by wedging the tip of the bronchoscope into a lobar bronchus and gently instilling 1 ml/kg (maximum 20 ml) of room temperature 0.9% saline under direct vision. The saline had been immediately aspirated into a sterile suction trap. Lobes were sampled in a set order: right upper, right middle, right lower, left upper, lingula and left lower. The samples had been sent to the microbiology laboratory for semi-quantitative bacterial culture. Cytology studies were not performed. Each BAL sample was used to inoculate 5 agar plates: one blood agar, one chocolate agar, one cysteine lactose electrolyte deficient agar, one sabouraud agar and one *Staphylococcus aureus* selective chromogenic agar. The plates were incubated for 48 hours. Visible growth was identified and categorised as: no growth, scanty growth, moderate growth or heavy growth. After each bronchoscopy, the bronchoscope was manually cleaned with detergent/enzymatic solution at the bedside and then reprocessed using an automatic endoscope reprocessor. The bronchoscope was reprocessed before use. Weekly surveillance swabs had been taken from the scopes which were always negative.

Results

All 50 children had FB-BAL and a CXR. The median (IQR) age of the children was 2.9 (1.7–4.4) years and the median (IQR) duration of their cough was 11.0 (8.0–14.0) months. Positive cultures were obtained from 41/50 (82%) of children; the total number of positive cultures was 64. Of those with positive cultures, 25 children (61%) grew 1 organism, 9 (22%) grew 2 different organisms and 7 (17%) grew 3 or more different organisms. The most commonly cultured organisms were: *Haemophilus influenza* (25 children), *Moraxella catarrhalis* (14 children), *Staphylococcal aureus* (11 children), and *Streptococcus pneumonia* (8 children). There was no relationship between the number of lobes with a positive culture and the culture quantity. Only 15 (30%) of the CXR were reported as normal. The most common abnormalities were bronchial wall thickening in 24 children (48%), increased bronchial markings in 10 (20%) and consolidation in 7 (14%).

If we had only sampled the most affected or the RML (as per the ERS guidance), 17 organisms (28 positive cultures) would have been missed in 15 children. None of these 15 children had a most affected lobe identified radiologically or macroscopically during the FB-BAL procedure. The RML result was therefore used. Eight of the 15 children had no organisms cultured from the RML. Only sampling a single lobe would therefore have led to 7 (14%) children having incomplete microbiological information and 8 (16%) having a false negative bronchoscopy result. If we had limited sampling to the lingula and the RML then 11 organisms (13 positive cultures) would have been missed in 10 (20%) patients, 6 (12%) of whom would have had no organisms cultured at all. See Table 1.

All 41 patients with a positive BAL culture were treated with a 6 week course of oral antibiotics. The most commonly prescribed antibiotics were co-amoxiclav (n = 24, 59%), clarithromycin (n = 5, 12%), amoxicillin (n = 4, 10%) and flucloxacillin (n = 4, 10%). Two of the organisms had in-vitro resistance to co-amoxiclav and 11 patients' isolated *Staphylococcus aureus* which our microbiology department recommends treatment with flucloxacillin or clarithromycin rather that co-amoxiclav.

Discussion

FB-BAL with the sampling of 6 lobes (including the lingula) has previously demonstrated a heterogeneous distribution of bacteria within the lungs of children with CF. [10] The data from the current study suggest that there is similar heterogeneity in the bacterial distribution in PBB. Due to this heterogeneity, if we had limited our sampling to one or two lobes a number of organisms would have been missed. This would have resulted in incomplete microbiological data or false negative results and ultimately the wrong antibiotic being prescribed or antibiotics being withheld completely. We have demonstrated that positive cultures were obtained from 41/50 (82%) of FB-BAL procedures. This is higher than the rates of 46% and 63% seen in previous studies in which only a single lobe was sampled. [11,12] Our higher rate of positive cultures seems to be related to the sampling of 6 lobes as if we had only sampled one lobe (RML) the percentage of culture positive procedures would have fallen to 33/50 (66%) and if we had sampled 2 lobes (RML and lingula) it would have been 35/50 (70%).

When performing a triple aliquot BAL, it is recommended that the 1st aliquot is sent for microbiological culture as this is a more proximal sample. [9] The 2nd and 3rd aliquots are pooled for cytology and non-cellular studies as they are more distal samples. When undertaking single aliquot bronchial washings it is not therefore appropriate to send cytology studies. If BAL cytology is undertaken in patients with PBB it demonstrates elevated neutrophil counts. [3] In some clinical situations this could be used to confirm that a positive BAL culture is caused by infection and not colonisation but as all patients with PBB are symptomatic, no positive airway culture could be presumed to be due to colonisation. This means that cytology results are not included as a diagnostic criterion for PBB and we do not think they would have provided any additional information in this particular clinical setting.

The mainstay of PBB treatment is oral antibiotics, although the use of intravenous and nebulised antibiotics has been reported. [11] If there has been microbiological confirmation of PBB then the antibiotics can be chosen according to the isolated organism and its sensitivities. If treatment is being started "blind" then co-amoxiclav is the most widely used first-line treatment. [13] When this cannot be used, a macrolide or cephalosporin are other options. [14] In our study, although co-amoxiclav would have been an appropriate antibiotic for most of the children, the bronchoscopy results led us to using a different antibiotic in 17. For 4 children the cultures enabled us to prescribe amoxicillin rather than co-amoxiclav. Two isolated organisms with in-vitro resistance to co-amoxiclav and 11 children isolated *Staphylococcus aureus* which our microbiology department recommends treatment with flucloxacillin or clarithromycin rather than co-amoxiclav.

In summary, this study confirms that FB-BAL is a useful investigation in children with PBB and the results can influence management. It also suggests that when undertaking FB-BAL in such children, a number of organisms may be missed if sampling is limited to one or two lobes. Further studies are required to evaluate the most appropriate timing of bronchoscopy in children with PBB and the optimal duration of treatment.

Author Contributions

Conceived and designed the experiments: FJG MS WL. Performed the experiments: KB JP SC JA FJG. Analyzed the data: RN. Contributed to the writing of the manuscript: RN FJG JA MS WL.

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Mini-Symposium: Recurrent Lower Respiratory Tract Infections

'Recurrent lower respiratory tract infections' – going around in circles, respiratory medicine style

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EDUCATIONAL AIMS

The reader will be more aware:

- of the probable importance of biofilms in the causation of persistent bacterial bronchitis
- that 'recurrent pneumonias' may represent exacerbations of bacterial bronchitis – episodes of bronchopneumonia
- of the increasing evidence of complex interactions between different pathogens, the 'normal' resident microbiota, viruses and host responses
- that bacteria may have very different effects in the two compartments of the lower airways – the conducting airways and the respiratory compartment
- that lack of accurate, simple diagnostic tests has contributed to erroneous fashions in pulmonary medicine which miss the subtleties of interactions involving, amongst others, the host, pathogens and allergens

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SUMMARY

Recurrent lower respiratory tract infections are very common in childhood, particularly the pre-school years. The term lower respiratory tract infection [LTRI] is, as with many terms used in respiratory medicine, used very loosely and carries little more information than the often decried term 'chest infections'. LRTIs should more accurately be characterised by

- the type of infection [viral or bacterial]
- the site of infection [conducting airways, or respiratory compartment or both - bronchitis/pneumonia/bronchopneumonia]
- the nature of the episode [acute or acute on chronic (exacerbation)]
- the interaction with co-morbidities such as asthma

The limited nature of the responses of the lower airways to any insult whether it is infective or irritation due to inhaled or aspirated chemicals means that almost any aetiology can lead to cough, shortness of breath and noisy breathing. We lack good non-invasive techniques to study the nature of the inflammation in the lower airways and hence the cause of chronic and recurrent symptoms in patients is frequently mis-diagnosed.

INTRODUCTION

With the benefit of hindsight the past 30 years is likely to be seen as a period in which those working in respiratory medicine, with the best of intentions, have propagated a number of erroneous and simplistic paradigms which have held back our understanding of the true nature of the spectrum of common respiratory illnesses in childhood. The two prime examples in paediatric respiratory medicine are forgetting that 'all that wheezes is not asthma' and that children, as well as adults, do suffer from persistent and/or recurrent bacterial bronchitis. In the 1990's we had to re-invent 'wheezy bronchitis' [a child who wheezes with a viral lower respiratory tract disease but who does not appear to have 'asthma'] and in the past decade, and against much resistance, we have had to re-discover the notion that a chronic wet cough in childhood has a high probability of being the consequence of a persistent bacterial

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bronchitis. This entity now appears in cough guidelines[1,2] and as a differential diagnosis of asthma in the SIGN/BTS asthma guidelines[3] though there are a significant number of clinicians who still appear to deny its existence as a clinical entity. One of the difficulties is the range of terms used to describe this biofilm disease[4,5] with terms such as suppurative lung disease, chronic bronchitis of childhood, pre-bronchiectais [when there are no diagnostic CT findings] and chronic endobronchial infection all being used to describe the same process.

The importance of persistent bacterial bronchitis in the context of this mini-symposium is that many 'recurrent chest infections' are probably exacerbations of a persistent bacterial bronchitis and in some these exacerbations which are associated with extension from the conducting airways into the respiratory region – a true bronchopneumonia. A chest X-ray taken at the time of an exacerbation may show varying degrees of opacities suggestive of alveolar consolidation and the episode may be labelled as an acute pneumonia if care is not taken to elicit the history of a chronic cough. While the 'pneumonic' component of such episodes responds rapidly to antibiotic therapy, eradicating the bacterial bronchitis is much more difficult as has been highlighted in studies involving patients with cystic fibrosis in whom these phenomena are well described.[6,7]

'RECURRENT CHEST INFECTIONS' DUE TO EXACERBATIONS OF ASTHMA - THE FALL AND RISE OF WHEEZY BRONCHITIS

The clinical entities of 'wheezy bronchitis' and 'chronic bronchitis' in childhood would have been only too familiar to clinicians in the 1950's, 1960's and early 1970's, that is in the pre/early antibiotic and pre-inhaled corticosteroid [ICS] era. Studies from the UK[8] and Scandinavia[9] in that period had indicated that wheezing with respiratory viruses in early childhood was relatively common and had a good long term prognosis. Inhaled corticosteroids in the form of beclomethasone became available in the mid 1970's[10] and transformed the lives of asthmatic patients. However, the use of ICS for the treatment of asthma in children remained very low with figures from the UK by the mid 1980's suggesting that approximately 1% of primary school children were being treated with ICS's while epidemiological studies suggested that perhaps 10% of the population would benefit[11,12]. The significant under diagnosis of asthma in school age children was associated with the widespread use of antibiotics to treat *'chest infections'*. Respiratory clinics at that time were relatively straight forward in that the commonest referral was children referred with a possible diagnosis of immunodeficiency for *'recurrent chest infections'* having had many courses of antibiotics. Commencing the children on 200 mcg of beclomethasone twice daily would lead to transformation of the child's health and an a parent who thought we were wonderful as they had a 'new child' – this dramatic and unequivocal response is what is required to make a definite diagnosis of asthma. Unfortunately, for those in secondary care the primary care physicians learnt this trick over the next decade and few children, in the UK at least, reach a secondary care respiratory clinic without having been labelled as 'asthmatic' and having received a trial of asthma medication.

The push in the mid 1980s onwards to ensure that asthma was considered in all those with recurrent chest symptoms or 'recurrent chest infections' clearly led to a significant improvements in the quality of life for many children with asthma but as so often occurs in medicine there were other unfortunate, unintended consequences that led to over diagnosis, unnecessary morbidity and inappropriate treatment for many other children. This is reflected in the referrals to respiratory clinics which are in the main now for 'difficult asthma', 'persistent cough' and, again, 'recurrent chest infections'.

The greatest difficulty we have in respiratory medicine is that we have few diagnostic tests and diagnosis frequently relies on a high quality history and appropriate response to therapy. For example we do not know what asthma is – we know that it can cause shortness of breath, wheezing, coughing and is often, but far from universally, associated with atopy. However many who report shortness of breath on exercise, persistent or recurrent coughing or who are atopic do not have asthma.

Two key features of asthma appear to be reversible bronchoconstriction (other than during an exacerbation when by definition the bronchodilators do not lead to a very rapid relief of bronchoconstriction)[13] and on going airways hyper-responsiveness that is significantly reduced by regular corticosteroid therapy thought to be mediated through their 'anti-inflammatory' effect. A diagnosis of asthma can only be made with a dramatic and unequivocal response to asthma medication. This might be >15% improvement in FEV1, a dramatic rapid relief of respiratory distress with a β agonist or a dramatic and unequivocal response to ICS over 6 weeks. We do not have a diagnostic test as for example a blood sugar in patients with diabetes mellitus[DM]. There are many causes of perceived polydypsia and polyuria, not least habitual excessive drinking in children but we do not need a trial of insulin to make the diagnosis of DM.

As we are reliant on the response to treatment we must be aware that we are anticipating an unequivocal response as the phenomenon of *regression to the mean* means that when any treatment is commenced or indeed if no treatment is commenced during an exacerbation of a child's symptoms [be it cough or perceived shortness of breath] they will inevitably improve to some extent in the coming days and weeks. The categories of *possible asthma*, *probable asthma* and *definite asthma* are valuable in that a patient should not be labelled as having definite asthma until the parents report that the response to treatment is dramatic and unequivocal – that is they have a 'new child'.

EXTRAPOLATING FROM SCHOOL AGE INTO PRE-SCHOOL CHILDREN

One area in which the drive to ensure that the issue of under diagnosis was addressed that caused particular problems was the extrapolation of the findings in school aged children into preschool children. There was large push by 'opinion leaders' to avoid the under diagnosis of asthma in all age groups and intervene early as this might 'modify' the natural history of the disease – a view actively supported by some of the pharmaceutical companies. Hence the term 'wheezy bronchitis' became a politically incorrect term and many argued that all wheezing episodes should be labelled as asthma contributing to the enormous increase in 'asthma admissions' during the subsequent decade. This increase in 'asthma' admissions particularly seen in pre-school children was mirrored almost perfectly by a fall in other respiratory diagnoses,[14] supporting the suggestion that much of the 'asthma epidemic' was attributable to diagnostic transfer.

Epidemiological studies in the 1990's in the UK[15] and USA,[16] replicated work from the early 1960's indicating that many children who wheeze in the first few years of life grew out of these symptoms and terms such as 'early transient wheeze', 'wheeze associated viral episode' etc were devised to reintroduce distinction between those with asthma (people to respond dramatically and unequivocally to asthma medication) in whom bronchospasm is a major component of the airways obstruction and those who simply wheeze with viral infections, the airways obstruction presumably being due predominantly to airways secretions and mucosal oedema – again a distinction clearly described some 50 years ago.[17]

The validity of many epidemiological studies are of course greatly limited by the poor understanding amongst clinicians and the wider public of what 'wheeze' is.[18] A wheeze is generated in response to a change in lung function leading to flow limitation. As

a result of flow limitation more energy is applied to the system than can be translated into movement of air and excess energy is then dissipated through vibration of central airways generating a musical sound known as a wheeze. A wheeze does not imply asthma nor indeed bronchoconstriction per se. Indeed poorly controlled asthmatics with chronically reduced lung function often are not wheezy presumably because of changes in respiratory patterns to minimise the wasted energy manifested by wheeze. This may well be the origin of breathing pattern disorders in many asthmatic patients, a co-morbidity that frequently exacerbates the underlying problem. Questions such as *'has you child wheezed or made a whistling sound?'* invites a positive response even if the noise the child makes is not a musical sound. An extreme example of the lack of precision in the utilisation of the term wheeze was in one publication attempting to argue that early colonisation of the upper airway may be associated with asthma in later life: *'Wheeze was defined to the parents as wheezing or whistling sounds,* **breathlessness, or persistent troublesome cough** *severely affecting the well-being of the infant or child'.*[19]

Having gone almost full circle in little more than a decade we have unfortunately added levels of complexity which are again causing confusion and taking us back towards a period of under diagnosis. An obsession with 'phenotypes of wheezing' such as early transient, persistent, and late onset transient[20] takes us away from the key question: Does a patient have asthma and benefit from appropriate treatment or do they have another cause for their persistent / recurrent symptoms? Recent guidelines suggesting that one should not use the term 'asthma' in pre-school children[21] seem likely to take us back around the circle from over use of asthma therapy in those with 'wheezy bronchitis' to under diagnosis of asthma in those who have it and would benefit from therapy and quite possibly to clinicians describing an exacerbation as 'just a chest infection'. Asthma can commence at any age – 10 months of age or 60 years of age and epidemiological studies have suggested that those with early onset 'true' asthma tend to have the most problems throughout childhood[15] [accepting that they are a minority of those who wheeze in the first couple of years of life]. If a child's symptoms are suggestive of asthma a diagnosis can be made reliably with a dramatic and unequivocal response to therapy. However, this requires the physician to review at the appropriate time after initiating therapy and to re-visit the diagnosis regularly as asthma is much more dynamic in childhood than in adulthood and many will cease to experience problems either permanently or transiently.

THE FALL AND RISE OF BACTERIAL BRONCHITIS

The vast majority of children with asthma are now looked after in primary care. An accurate diagnosis and appropriate treatment transforms the lives of the vast majority of asthmatic children and those in secondary care should not forget the impact of appropriate treatment. Of those referred to secondary care with 'difficult asthma' there are generally only three causes:

- It is not asthma
- It is asthma and something else
- It is asthma but the medication is not being delivered to the lungs regularly
  - Poor regimen compliance [adherence] – not taking the prescribed doses
  - Poor device compliance [not using the device effectively due to lack of competence or contrivance – knowing how to use the device but contriving to use it in an alternative ineffective manner]

It has become increasingly recognised that one of the commonest causes for a mis-diagnosis and as a co-morbidity is a persistent bacterial bronchitis. Once again we have come full circle having spent a period denying the very existence of a major cause of respiratory morbidity. There have been numerous studies addressing the prevalence of 'wheeze' but chronic cough has largely been neglected despite the fact that reviews of published studies indicate that 10% or more of children experience a chronic cough[22] and the few studies addressing this issue amongst children reaching secondary care have found the commonest cause to be persistent bacterial bronchitis.[4,23,24]

Over the past decade we have had to revisit the subtle clinical differences between those who have asthma and bacterial bronchitis acknowledging that in a number of children, both co-exist. This is presumably due to mucus plugging and impaired mucociliary clearance in poorly controlled asthma acting as significant risk factor for bacterial colonisation.

BIOFILM DISEASE OF THE CONDUCTING AIRWAYS

In addition to the reinventing of the basic clinical understanding that the condition exists, we have, through the work of interested clinicians and basic scientists, been able to clarify the processes that contribute to this form of disease through improved understanding of the behaviour of pathogens resident in biofilms on the epithelium of the upper airways [including middle ear and sinuses] and the conducting airways.[7,25–27] These insights provide a scientific basis on which we can start to understand the nature, treatment and most importantly, the prevention of this chronic condition.

When antibiotics first became widely available they were embraced by physicians in primary and secondary care, presumably because of the perceived benefits to their patients. As with every 'magic bullet', the benefits seen in those with conditions such as persistent bronchitis led to their over use and a prescription became almost standard for any child with lower respiratory tract symptoms. However it is of note that the widespread use of antibiotics through the 1970's, 1980's and into the 1990's appears to have coincided, and probably led to, the almost disappearance of bronchiectasis in many Western Countries, though world wide it remains an enormous cause of morbidity.

The vicious circle hypothesis of bronchiectasis[28] implicitly implicates a period of persistent bacterial bronchitis as the driving force for the chronic inflammation that eventually creates sufficient damage to appear as bronchiectasis on a CT scan.[24] This is the theoretical basis for our aggressive antibiotic therapy in cystic fibrosis which has been associated with delaying the progression of bronchiectasis and greatly improved survival figures. The aggressive eradication regimens attempting to prevent the establishment of pseudomonal biofilms has been a key development in the past 20 years.[7] Also implicit in the vicious circle hypothesis is the concept that impaired mucociliary clearance permits the establishment of bacterial 'colonisation' and hence biofilm formation. The impairment to mucociliary clearance may be post a viral lower respiratory tract infection or pertusis when cilia take many weeks or months to fully recover; mucus plugging as occurs in asthma, relative dehydration of the mucocilary layer as in cystic fibrosis [CF]; structural as in patients with tracheomalacia; impaired cough as in neuromuscular disease or is in itself secondary to bacterial infection observed in patients with significant immunodeficiency.

BACTERIAL INFECTIONS AND LUNG COMPARTMENTS

In order to understand the role of bacterial biofilms in the causation of pulmonary infections it should be remembered that the lower airways has two compartments:

- the conducting airways to generation 16
- the distal respiratory compartment [generations 17-23].

The latter serves the fundamental purpose of the lungs which is to exchange carbon dioxide and oxygen. The structure of this region is very different to that of the conducting airways which serve two principle functions. Repeated divisions permit the establishment of a huge cross sectional area in the respiratory compartment to facilitate gas exchange. Its structure with a stratified epithelium, mucus and goblet cells, cilia and resident macrophages functions to help protect the lower airways from invading pathogens which are generally removed by resident macrophages or by mucociliary clearance.

A bacterial infection in the respiratory compartment, a bacterial pneumonia, is generally an acute illness associated with high fever associated with rapid replication of organisms such as *streptococcus pneumoniae* and *haemophilus influenza [HI]*, including non-typable HI, which resolve very rapidly with the commencement of antibiotic therapy unless there is a complication such as empyema.

The same organisms can infect the conducting airways but usually require an opportunity such as those provided due to impaired mucociliary clearance secondary to one of the conditions noted above such as a viral bronchitis with damage to the ciliated epithelium. Once established in sufficient quantities the organisms can establish biofilms in which replication occurs at low levels but organisms remain for prolonged periods within structures that provide protection against host responses and other organisms. The interactions between organisms such a strep pneumoniae, non-typable HI and *staphylococcus aureus*[26,27,29–32] in which they can compete for a niche or collaborate are just beginning to be understood. Indeed the competition between *Staphylococcus aureus* and the other organisms has been proposed as one possible approach to controlling *methicillin resistant staphylococcus aureus* [MRSA]. The interactions with viral pathogens also appears to be important with many exacerbations amongst patients with bronchiectasis, chronic obstructive pulmonary disease [COPD] and bacterial bronchitis and hence many *'recurrent chest infections'* being associated with apparent viral respiratory tract infections. The exacerbations that accompany a viral respiratory tract infection may be the consequence of planktonic forms of the bacteria being released from the biofilms under circumstances that favour dissemination.[33] The increase in symptoms may be due to the increased inflammatory response associated with increased bacterial load or in response to the early stages of further biofilms being established in previously unaffected areas though the exact mechanism is unknown.

NORMAL MICROBIOTA, 'COLONISATION' WITH POTENTIAL PATHOGENS AND BIOFILMS

Our understanding of the interaction of bacteria for good and ill is starting to accelerate due to new concepts and techniques. In particular we are beginning to realise that there is likely to be a vast resident flora lining the upper[34] and probably the lower airways[35] in health that is not identified by traditional microbiological techniques. 'Infection' with traditional pathogens,[4,5,23,24,36] appears to follow 'colonisation' of the upper airways and this process is now being revealed as being much more complex than our previous simplistic understanding of bacteria simply residing for periods in the upper airways and then disappearing. We are just beginning to understand that the pathogens identified using traditional microbiological techniques interact with not only the host but also a much wider range of non-culturable organisms and with other recognised pathogens. Even the idea that such 'colonisation' is asymptomatic is disappearing. Understanding of the importance of biofilms to many bacteria is also providing insights into potential ways of preventing and treating chronic bacteria mediated diseases of the airways. Developing virulence factors that contribute to severe local or invasive disease is presumably beneficial in the short term but usually comes at some biological cost.

CLINICAL FEATURES AND *'RECURRENT CHEST INFECTIONS'* ASSOCIATED WITH PERSISTENT BACTERIAL BRONCHITIS

The disease caused by biofilms within the conducting airways is a chronic disease characterised by a persistent cough,[4,5,23,24,37] [though in the milder forms the cough may disappear intermittently, particularly in the summer]. This is typically worse with change in posture such as occurs just after going to bed or first thing in the morning on rising, but with more severe cases the cough persists through the night and is present during the day, particularly with exercise and the children may cough sufficiently to appear short of breath. The cough is typically wet though our unpublished study confirms the suggestion 'that one person's wet cough is another persons dry cough' and the question *'does he/she sound like 50 a day smoker first thing in the morning'* is often easier for parents to understand. Unless there are substantial amounts of secretions it is normal for the chest to be 'clear' on auscultation – exactly as is the case with young cystic fibrosis patients experiencing and exacerbation. However coarse, predominantly inspiratory, sounds are heard with increased airways secretions and not infrequently referred to as 'wheeze.

As noted above exacerbations ['recurrent chest infections'] usually occur with inter-current viral infections, again mimicking asthma. Hence the initial history may be very suggestive of asthma in that the child is reported to cough at night, get short of breath with exercise and to be terrible with colds and it is only with more careful exploration of the symptoms that they might be distinguished and indeed even then it may be difficult. Ultimately the diagnosis is based on an appropriate dramatic response to treatment at the appropriate time. For PBB it typically takes 2 weeks of treatment using high dose of antibiotics such as amoxicillin + clavulinic acid [40mgs /kg/ day amoxycillin content in two divided doses] for the cough to resolve. Quite what to do then is unclear as the airway presumably remains unhealthy and recolonisation is the frequent if antibiotics are stopped at this point. Prolonged courses of antibiotics are frequently used, but which antibiotic and the optimal duration of treatment in the first instance has yet to be determined. The condition is associated with substantial morbidity both during exacerbations[38] and during the interval periods[39] not least because of failure of clinicians to recognise the condition.

Non-invasive techniques for identifying viral and bacterial pathogens as well as characterising the pattern of inflammation within the lower airways are urgently required. Clarification of the role of bacteria in the causation of chronic symptoms and the associated, frequently viral, induced exacerbations which probably account for many of the 'recurrent lower respiratory tract infections' will be an important step in improving our treatment and prevention of these pathogen induced diseases.

PRACTICE POINTS

- careful assessment of children with recurrent and persistent pulmonary symptoms is required to ensure that appropriate therapy is instituted
- a diagnosis is generally suggested by the history but only confirmed [in the absence of diagnostic tests] by a dramatic and unequivocal response to therapy
- bacterial bronchitis is an important co-morbidity and alternative diagnosis in some patients diagnosed with asthma

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