Journal of Antimicrobial Chemotherapy (2002) **49**, 31–40

JAC

Review

Antibiotic therapy of community respiratory tract infections: strategies for optimal outcomes and minimized resistance emergence

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Widespread, increasing antibiotic resistance amongst the major respiratory pathogens has compromised traditional therapy of the major infective respiratory syndromes, including bacterial pneumonia and acute exacerbations of chronic bronchitis. Guidelines for antibiotic prescribing dating from the 1980s to 1990s, which attempted to address such problems, were commonly too prescriptive and difficult to apply, and took little account of end-user practice or locally prevalent resistance levels. Further confusion was caused by conflicting recommendations emanating from differing specialty groups. The evidence that such guidelines benefited either clinical outcomes or treatment costs has been disputed. They have probably had little effect on resistance emergence. We report the recommendations of an independent, multinational, inter-disciplinary group, which met to identify principles underlying prescribing and guideline formulation in an age of increasing bacterial resistance. Unnecessary prescribing was recognized as the major factor in influencing resistance and costs. Antibiotic therapy must be limited to syndromes in which bacterial infection is the predominant cause and should attempt maximal reduction in bacterial load, with the ultimate aim of bacterial eradication. It should be appropriate in type and context of local resistance prevalence, and optimal in dosage for the pathogen(s) involved. Prescribing should be based on pharmacodynamic principles that predict efficacy, bacterial eradication and prevention of resistance emergence. Pharmacoeconomic analyses confirm that bacteriologically more effective antibiotics can reduce overall management costs, particularly with respect to consequential morbidity and hospital admission. Application of these principles should positively benefit therapeutic outcomes, resistance avoidance and management costs and will more accurately guide antibiotic choices by both individuals and formulary/guideline committees.

Introduction

Almost 10% of the worldwide burden of morbidity and mortality relates to respiratory tract infections (RTIs) and, whilst the majority of this is viral in aetiology, three-quarters of all antibiotic consumption is for RTIs.[1] In the context of considerations for improving therapeutic outcomes, reducing resistance emergence/prevalence and minimizing costs by limiting and optimizing therapy, respiratory infections are clearly an appropriate area for action.

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Streptococcus pneumoniae is the most common bacterial pathogen in RTI and each year is implicated in 500 000 cases of pneumonia and over 7 million cases of otitis media in the USA alone.[2] Worldwide, pneumococcal disease is among the leading cause of mortality, particularly among children, the elderly and those with co-morbid illness.[3] Increasing penicillin/macrolide resistance, reaching 30–40% of isolates in many areas, is therefore of considerable concern.[4] Macrolide resistance in *S. pneumoniae* now exceeds penicillin resistance in some regions and continues to increase.[3,4] Pneumococcal fluoroquinolone resistance remains rare, but will inevitably increase as these agents are more widely employed in RTI.[4–7]

The selection of antibiotic resistance is inevitable. The overall volume of antibiotic prescribing is the primary factor driving resistance at both local and regional levels,[8–11] although other influences, notably clonal spread, complicate epidemiology. It is therefore necessary to educate prescribers in the need to avoid antibiotic therapy where there is no clinical indication, although this may be resisted by patients, who will also require education.[12,13] However, although studies of pneumococcal disease in Scandinavia have indicated significant falls in resistance levels to a specific antibiotic after reduction in its prescribing,[14–16] prescribing of structurally unrelated antibiotics (via co-selection of multi-resistance plasmids and other resistance traits) may perpetuate selection pressure.[17]

Guidelines on antibiotic prescribing in RTI are available almost in profusion. For community-acquired pneumonia (CAP) alone, they include those of the American Thoracic Society (ATS), the Infectious Diseases Society of America (IDSA), the British Thoracic Society (BTS), the European Respiratory Society (ERS) and many other national societies and organizations.[18–22] Their recommendations vary, reflecting the inadequacies and ambiguity of the available evidence base, bacterial resistance rates and both inter-specialty and national differences.[18–22] Compliance with guidelines is neither universal nor optimal,[23,24] nor have existing guidelines necessarily improved outcomes or reduced costs. In one study of CAP, in 46% of cases ATS guideline compliance made no difference to mortality, but increased drug acquisition costs 10-fold in more severe disease.[23]

Lack of compliance with guidelines may result from lack of awareness, inertia, ambiguity and inconsistency of validation, variance in local resistance prevalence and prescribing patterns, interference via marketing activities and absence of enforcement measures.[24–26] Primarily, however, physicians must perceive guidelines as being relevant and useful to their everyday clinical practice.

The consensus principles reported in this paper represent the conclusions of an international, interdisciplinary group that considered the current evidence supporting appropriate use of antibiotics in lower respiratory tract infection (LRTI).

Antibiotics are indicated only in bacterial infection

This is self-evident but commonly ignored. The reasons driving the unnecessary and excessive prescription of antibiotics are complex, but include pressures from patients and parents, and constraints on physician time, plus a lack of appreciation of the possible impact on resistance.[12,13] Nurse prescribing, a projected development in Europe, may also contribute to excessive use in the future. In the UK the Medicines Control Agency (document MLX 273, 2001) has already consulted on extending prescribing of prescription-only medicines, including oral antibiotics, to nurse practitioners.

Use of antibiotics for non-bacterial or self-limiting bacterial infection risks adverse reactions and selects for development of bacterial antibiotic resistance. The latter is inextricably linked to antibiotic consumption at both local (individual practice) and regional levels,[8–11] and increases healthcare costs via unnecessary acquisition cost, adverse event management and resistance emergence.[27] Nevertheless, there is considerable unnecessary use of antibiotics,[28–30] notably in viral infections such as the common cold.[31] In Canadian children, acquisition costs of unnecessary antibiotic prescribing were almost 50% of total prescribing costs.[28]

Prescribing of antibiotics for respiratory infection, whether necessary or not, may also have collateral effects on microbial flora elsewhere in the body, notably the bowel. Thus, restriction of use or, conversely, overuse may have beneficial or deleterious effects on other diseases, such as urinary tract infection, via susceptibility patterns of associated pathogens.

Diagnostic and other measures to reduce prescribing

Correct diagnosis of bacterial infection is the key to limiting unnecessary prescribing. However, lack of availability of cost-effective diagnostic tests ensures the persistence of 'grey areas' of confusing aetiology. Therefore, guidelines should offer practical criteria to identify those bacterial infections that require antibiotic therapy.

Thus, although initially viral, 60% of patients with symptoms of sinusitis persisting for 10 days have bacterial infection.[32] Restriction of therapy to only those patients would significantly reduce unnecessary prescribing.[33] Similarly, restriction of antibiotic therapy in otitis media to those children with acute bacterial disease and avoidance in otitis media with effusion (unlikely to indicate bacterial infection) could reduce unnecessary use by two-thirds.[34,35] Moreover, there is little evidence that antibiotic therapy influences the outcome of acute bronchitis or milder exacerbations of chronic bronchitis,[31,36,37] and prescribing could again be dramatically reduced. Thus more precise diagnostic criteria can improve the quality of therapy.

Measures to reduce the prevalence of bacterial infections are also relevant. For example, conjugate pneumococcal and influenza vaccines should reduce the frequency of CAP and acute exacerbation of chronic bronchitis (AECB), particularly in elderly, at-risk populations,[2,38–40] and thus decrease antibiotic usage. Preliminary data indicate dramatic reductions in hospitalization and mortality from use of these vaccines,[41] suggesting an associated reduced necessity for prescribing.

Therapy should reduce maximally or eradicate the bacterial load

There is accumulating evidence to confirm bacterial eradication as the primary goal of antibiotic therapy and the main determinant of therapeutic outcome.[42] However, spontaneous clinical recovery, common in mild to moderate RTI, may mask differences in bacteriological effectiveness of antibiotics and allow sub-optimal agents to continue to be prescribed.[42,43] Thus, agents with poor bacteriological efficacy can appear clinically almost as good as those with optimal efficacy: the 'Pollyanna effect'.[43] However, these small differences, apparently irrelevant in small series, translate to significant numbers of bacteriological failures in larger populations treated with sub-optimal therapy, with resultant prolongation of morbidity, risk of resistance emergence and dramatic cost consequences.

Antibiotic therapy that allows bacterial persistence risks not only early recurrence or relapse but also resistance selection. It is therefore inappropriate. In practice, most empirical RTI therapy is clinically based and bacterial eradication is usually considered secondarily, if at all. However, bacteriological efficacy is the more sensitive and direct outcome measure, and clinical studies should aim at identifying reduction in bacterial load as the primary parameter by which antibiotics are compared.

In AECB, failure of bacteriological eradication predicts clinical failure[44] and such failure (and hospital admission) is more common with agents of lower intrinsic activity and higher resistance prevalence or where resistance develops during therapy.[45,46] Bacteriological efficacy may also influence longer-term outcomes in AECB, superior eradication of *Haemophilus influenzae* in patients receiving gemifloxacin compared with clarithromycin (82% versus 62%) correlating at 26 week follow-up with 29% and 42% relapse rates ($P = 0.016$), respectively.[47]

Pharmacodynamic indices assist appropriate choices of agent and dosage

Pharmacodynamic (PD) properties clearly differentiate between antibiotic classes, and often between members of the same class, in their ability to eradicate pathogens at drug concentrations attainable during therapy. Standard *in vitro* MICs give no information on the time-course of antibacterial activity, but integration of MIC with pharmacokinetic (PK) parameters provides PK/PD indices, which are valuable tools with which to predict antibacterial effects and optimal drug dosage.[48,49] Such indices include: the time for which non-protein bound concentrations exceed the MIC ($T >$ MIC); the ratio between peak serum concentration (C_{max}) and MIC (C_{max}/MIC); and the relationship between drug exposure [area under the serum 24 h concentration–time curve (AUC_{24})] and MIC (AUC_{24}/MIC).[48–52] These indices correlate with clinical outcome,[52–54] underlying bacteriological eradication[53,55] and emergence (or prevention) of resistance.[51,56] Attempts to integrate such indices with microbiological parameters other than MIC [e.g. mutant prevention concentration (MPC)] is, as yet, of unproven clinical relevance.[48]

For β-lactams and macrolides, bacteriological efficacy correlates with $T >$ MIC. Higher survival rates (>90%) are seen in animal models if $T >$ MIC is ~40% of the dosage interval for penicillins and 40–50% for macrolides and cephalosporins.[48] Human studies (in otitis media and sinusitis) support these findings.[48–51]

Fluoroquinolones exhibit concentration-dependent bacterial killing and, therefore, C_{max}/MIC[52] and the relative AUC/MIC ratios[53–55] correlate with efficacy for these agents. Based on human data from levofloxacin studies, a C_{max}/MIC ratio of at least 10–12 (*inter alia*) predicts optimal bactericidal activity for susceptible organisms.[52] Past work suggested an AUC/MIC ratio of ⩾125 to optimize outcome in pneumonia. However, *in vitro*, *ex vivo* and modelling studies (but as yet not human data) suggest an AUIC ratio of 25–30 to better predict optimal bactericidal efficacy for other fluoroquinolones against *S. pneumoniae*.[48,57,58] A recent review indicates that all fluoroquinolones, except ciprofloxacin in standard dosage, would exceed the AUC/MIC target (50) expected to achieve pneumococcal eradication in LRTI.[48]

Further human studies are required to examine the predictive quality of PD parameters on bacterial efficacy and resistance development in Gram-positive RTI in man. Nevertheless, PD principles can be used to determine thresholds for adequate dosage and to compare agents both within and between antibiotic classes. They should be used routinely in drug evaluation and might obviate repetitive and uninformative equivalence studies.[59]

Antibiotic choices must reflect local resistance prevalence

Increasing high-level resistance in RTI pathogens must inevitably result in increased therapeutic failure rates, but the true extent of failure in community-acquired RTI and its relation to resistance prevalence is currently unknown. Adequately documented resistance-related failures are few in number, but are certainly an iceberg phenomenon.

A research database to which such failures could be notified might rapidly have significant implications for guidelines. However, until such data are available, it must be accepted that bacteriological failure is most likely to result from sub-optimal therapy, irrespective of the 'degree' of resistance.

For example, in the rat pneumonia model, co-amoxiclav at doses mimicking standard paediatric dosage was ineffective against pneumococcal strains with MICs of >2 mg/L, although efficacy was maintained if the dose was increased and $T >$ MIC was at least 34%.[60] The impact of penicillin resistance differs between β-lactams, dependent on *in vitro* potency and PD characteristics. Thus, in gerbil otitis media, amoxicillin was significantly more effective than cefuroxime against a penicillin-resistant strain (MIC 2 mg/L).[61] Similar observations apply to fluoroquinolones. In the rat pneumonia model, grepafloxacin and gemifloxacin were significantly more effective against pneumococci than either levofloxacin or ciprofloxacin ($P < 0.01$).[62]

Double typanocentesis (tap) studies in human otitis media demonstrate the effect of antibiotic resistance on bacterial eradication. For example, in one study of penicillin-resistant isolates, failure rates were 4/14 (29%) with amoxicillin compared with 11/17 (65%) with cefaclor, which had a less favourable PD profile.[63] Increasing the $T >$ MIC of β-lactams by manipulating dosing schedules can increase their efficacy against resistant strains. For example, single-dose ceftriaxone failed to eradicate penicillin-resistant *S. pneumoniae* (PRSP) in 7/13 (54%) of patients, whereas 3 day therapy eradicated 94% of resistant strains ($P = 0.01$).[64]

These studies clearly indicate that the use of agents and dosages with optimal potential to eradicate pathogens is appropriate.

Prescribing change and choices of agents

Thus, locally relevant guidelines should reflect the prevalence and degree of resistance levels, and this may require modification of existing practice. Penicillin resistance in *S. pneumoniae*, although prevalent in many countries, has not yet compromised adequate dosage therapy of adult CAP in monomicrobial infections of moderate severity caused by strains with MICs of up to 2 mg/L.[65,66] In paediatric bacteraemia, no association was found between penicillin resistance and mortality.[67] However, others have reported increasing adult mortality in CAP related to pneumococcal penicillin MIC elevation[68] and mode MICs for pneumococci are rising: recent data from the USA reported 7.8–9.7% of strains to have penicillin MICs of $\geq$4.0 mg/L.[68,69] Strains with high MICs are often associated with identifiable risk factors and detected in hospital patients.[70,71] However, when they become common in the community, even maximal doses of penicillins may no longer prove effective and alternative strategies will be necessary.[72]

Macrolides may not prove to be satisfactory substitutes: treatment failure in CAP caused by macrolide-resistant pneumococci has been reported since early in the 1990s.[73] More recently, 11 patients with pneumonia and one without an identifiable infection site developed bacteraemia with a macrolide-resistant *S. pneumoniae* whilst receiving macrolide therapy. All responded to β-lactam therapy.[74] Four similar cases have subsequently been reported and a further four azithromycin failures, three treated successfully with a quinolone and one fatal, are recorded.[75–77] These probably represent the tip of an as yet clinically unapparent iceberg. However, there appears little doubt that macrolide resistance correlates directly with clinical failure and that guidelines should exclude macrolides in areas of rising resistance prevalence. This view is reinforced by a Finnish population study directly linking rising macrolide resistance to macrolide use ($P = 0.006$).[78]

New third-generation fluoroquinolones have markedly increased potency against pneumococci in comparison with second-generation agents, although most treatment failures with earlier agents were due to inadequate dosage, absorptive interactions or related severe underlying disease rather than lack of intrinsic activity. However, fatalities in meningitis[79] and clinical failures in pneumonia caused by levofloxacin-resistant *S. pneumoniae*[80] confirm that emergent resistance is becoming clinically relevant for agents with marginal PD indices.[6] Most recently, stepwise *parC* and *gyrA* mutations in pneumococci during ciprofloxacin therapy of RTI have been shown to be responsible for treatment failures and for associated jumps in MICs for later agents, such as moxifloxacin, in strains (23F) that have spread to other patients.[46]

Thus, there is increasing evidence from animal models and human infection that bacterial resistance influences outcome and that local surveillance should dictate optimal choices for empirical therapy. However, this is an intrinsically dynamic situation—perceptions of stasis result from inappropriate perspectives—which requires regular re-assessment.

Appropriate antibiotic choices to minimize resistance

Antibiotic resistance is inevitable. Therapeutic exposure of human bacterial pathogens to antibiotics exerts a continuous selection pressure on pathogens present both in infection and carriage or commensal sites in the individual, within institutions, the community and the environment. This has been recognized since the beginning of the antibiotic era[72] and favours pathogens that exhibit spontaneous resistance mutation and/or acquire genetic resistance determinants from other organisms. Antibiotic selection pressure may also accelerate bacterial chromosomal resistance mutation.[81] Sub-optimal dosage also predisposes to resistance emergence, e.g. lower than recommended dosage

and prolonged exposure to β-lactams predisposes to nasopharyngeal carriage of PRSP in children.[82]

Differential effects both between and within antibiotic classes have major importance. For example, increasing prevalence of PRSP in France is linked to widespread replacement of aminopenicillins by oral cephalosporins, many of which achieve a $T >$ MIC of <40% for *S. pneumoniae*, resulting in inadequate bacterial killing.[83,84] A significant correlation between macrolide resistance in *S. pneumoniae* and consumption of long half-life macrolides (clarithromycin, azithromycin) has been reported from various countries, even after single dose exposure.[85,86] The ability to select for resistance in tissue compartments and at specific concentrations (selective window) may also allow differentiation of agents.[87]

For fluoroquinolones, reports from Hong Kong, Canada and the USA indicate emergent quinolone resistance in pneumococci,[5–7] primarily mediated via chromosomal mutation. Thus increasing mutations lead to stepwise increases in resistance and increased prevalence of first-step mutants predisposes to selection of highly resistant second-step mutants.[88] Selection of first-step mutants might be avoided by restricting use of less active agents in favour of newer quinolones with better PD performance.[46,89] Nevertheless, levofloxacin, only marginally more potent against *S. pneumoniae* than ciprofloxacin, is widely and apparently effectively used, although the studies supporting such use were undertaken in the years prior to the current upward shift of pneumococcal quinolone MICs.[90–92] Thus, AUC/MIC and C_{max}/MIC ratios have become marginal in some patients with CAP,[93] which may result in sub-optimal efficacy and selection of first-step mutants.[46,56] Risk factors for acquisition of levofloxacin-resistant *S. pneumoniae* include presence of chronic obstructive pulmonary disease, residence in an institution and prior exposure to quinolones.[94]

Co-selection of resistance may be encouraged by sub-optimal exposure to other antibiotics. In Iceland, penicillin resistance was twice as likely to be associated with the use of co-trimoxazole or erythromycin than with β-lactams in association with three or more courses of antibiotic treatment.[95] In the UK, sulphonamide resistance (in *Escherichia coli*) remained high due to co-selection, despite dramatic reductions in prescribing.[17]

Active control of resistance by antibiotic restriction

In hospitals and other institutions, decreased antibiotic use may reduce the prevalence of resistance,[96] but the situation is more complex in the community. For example, in Finland, implementation of guidelines reduced macrolide consumption from 2.40 to 1.38 defined daily doses (DDD)/1000 population and the prevalence of erythromycin-resistant group A streptococci fell from 16.5% in 1992 to 8.6% in 1996.[16] However, a more recent Finnish study showed rising pneumococcal resistance to parallel increasing macrolide use.[78] In Iceland, carriage of PRSP in children was found to relate to age (<2 years), area of highest antibiotic consumption and recent individual use of antibiotics, including co-trimoxazole.[14,95] Reduced antibiotic use, particularly of co-trimoxazole, was accompanied by a decrease in the prevalence of penicillin non-susceptible strains from a peak of 19.8% in 1993 to 12.9% in 1997.[14]

Resistance prevalence can increase very rapidly in a population and mathematical models suggest that threshold levels exist, after which resistance dissemination accelerates rapidly.[9] Reduced antibiotic consumption results in a much slower decline in prevalence and, in areas with very high prevalence, it may be that reduction in antibiotic pressure will have an even slower effect, especially in the presence of multidrug resistance.[9,97,98] This provokes the chilling prospect that supra-threshold levels of community multi-resistance may no longer be reversible. In addition, the loss of virulence often associated with resistance may be overcome by compensatory mutation.[99,100] It is, therefore, imperative that appropriate strategies are acted upon prior to such events; later action may fail to redress the situation.

In Sweden, a programme to prevent the projected increase in prevalence of PRSP has incorporated contact tracing and isolation with efforts to reduce antibiotic consumption and, thereby, carriage and dissemination of resistant strains. Its effectiveness has not yet been established[15] and it may yet be pre-empted by interspecies transfer of resistance genes. The threat posed by the global resistance gene pool in related species must be anticipated. Assuming the continued transfer of genetic data from commensal streptococci to pneumococci and the involvement of later antibiotic classes,[101] such as the quinolones, the routine use of optimally active agents becomes a priority.

Acquisition costs may be insignificant compared with therapeutic failure

Drug acquisition costs are a primary consideration only if there are no significant differences in:

- treatment outcomes between agents;
- potential for selection of resistance;
- incidence of significant treatment-related adverse events.

This might, for example, occur with generic substitution of an established agent.

In many cases, cost-effectiveness analyses can identify appropriate options on the basis of least cost per outcome measure gained.[102] For example, quinolones may compare favourably with standard care of CAP in terms of costs of treatment, including specific values such as length of stay.[103,104] Alternatively, shorter courses of equal efficacy may minimize cost. In the UK, prescribing costs of 7 day

therapy of CAP with generic antibiotics in the 1990s exceeded the costs of 5 day therapy by £1.9–7.2 million.[25] Thus, if similar outcomes result, shorter courses are clearly preferable.

Inappropriate therapy of RTI is expensive. For example, in 49 552 episodes of LRTI where antibiotic treatment matched the susceptibility of the aetiological agent, the average cost per episode was US$8821, compared with US$14 754 when treatment was discrepant ($P = 0.02$).[105] In AECB, first-line agents (amoxicillin, co-trimoxazole, erythromycin, tetracyclines) gave failure and hospitalization rates of 19% and 18%, respectively, compared with 7% and 5% for agents with more optimal PD activity. The infection-free interval was significantly longer in the latter group and overall costs were almost halved (US$942 versus US$542).[45]

Treatment failure far exceeds the acquisition costs of any antibiotic[106] and hospitalization is the key cost-driver of management of moderate/severe pneumonia and AECB.[107] Excess costs of hospitalization following treatment failure far outweigh primary care costs.[108] In a study of 50 000 episodes of community-acquired LRTI, 65.6% (US$73.1 million) of the total management costs related to hospitalization, whereas drug acquisition costs were 5% (US$5.6 million).[109] Similarly, in AECB patients >65 years of age, hospitalization costs were $1.1 billion per annum compared with $24.9 million for outpatient costs.[110]

Few prospective studies have examined more long-term parameters of cost-effectiveness. Ciprofloxacin therapy of AECB was cheaper and had greater benefit on quality of life in patients with multiple risk factors for poor outcome than 'standard–usual care' therapy.[111] Thus, severity criteria may be used to indicate subgroups in which drugs with higher acquisition costs, but with improved PD potential may demonstrate cost benefit. A follow-up study of gemifloxacin compared with clarithromycin over 6 months in AECB[47] showed that higher rates of eradication of *H. influenzae* by the quinolone correlated with lower relapse rates (29% versus 41.5%; $P = 0.016$), a reduction in hospitalizations and a saving of US$329 per patient.[112]

Thus antibiotic treatment that reduces the risk of hospitalization or reduces length of stay must be highly cost-effective, and agents that achieve improved bacterial eradication also have the potential to improve long-term clinical outcomes and reduce overall costs and, perhaps, limit resistance emergence and dissemination.

Conclusions

From the 1980s onwards, resistance has steadily compromised standard therapy of bacterial LRTIs and, in consequence, newer agents, inevitably more costly, have been required. The use of these agents exposes them to risks of resistance emergence and patients to the risk of novel adverse drug reactions, which are phenomena having important implications in morbidity and cost for individuals and for society. However, antibiotic utilization continues to increase, perhaps more in some countries than in others[113] and, for RTI at least, >90% of patients expect antibiotic treatment[13] and may resist restricted prescribing. Optimized therapy must therefore be seen to be desirable and must demonstrably reduce morbidity (and mortality), the costs of failure and hospitalization, and emergence of antibiotic resistance. Strategies most likely to achieve these goals must incorporate the principles summarized below:

- identification of bacterial infections by optimized diagnosis;
- severity assessment where relevant;
- recognition and incorporation of ambient resistance data;
- targeting bacterial eradication (or maximal reduction in bacterial load);
- use of PD indices to optimize choice and dosage;
- objective assessment of true (overall) costs of resistance and related treatment failure.

It is very clear that many practice guidelines meet neither these principles nor the interdisciplinary, evidence base-linked criteria that might strengthen the provenance of the guideline concept.[114] Lack of credibility is one of the primary failures of speciality group advocacy guidelines, followed rapidly by lack of relevance to everyday practice,[24] family practice guidelines in other disciplines often having had minimal impact on patient outcomes.[115] Such findings have followed more than a decade of guideline development. Perhaps a radical re-evaluation of the principles of therapy in our own discipline is also long overdue.

Acknowledgements

The authors are grateful to colleagues who have made various contributions to this paper. These include Drs Jack Anon, William Craig and John Langan. The Group also wishes to acknowledge the valuable editorial contribution of Caudex Medical personnel, notably Naomi Richardson, and is grateful to GlaxoSmithKline plc for financial support.

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