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Summary of Selected Presentations

ELAIR3

Mexico City, Mexico, 2017

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FACING THE WORLDWIDE THREAT OF ANTIMICROBIAL RESISTANCE

A narrative summary of selected presentations that took place on 11th–12th May 2017, as part of the Encuentro Latinoamericano de Infecciones Respiratorias Recurrentes (ELAIR) educational event in Mexico City, Mexico

Speaker
Javier Garau

Hospital Universitari Mutua de Terrassa, Barcelona, Spain

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MEETING SUMMARY

The third Encuentro Latinoamericano de Infecciones Respiratorias Recurrentes (ELAIR) took place in Mexico City, Mexico, on 11th–12th May 2017. ELAIR brought together experts from across Latin America and further afield, continuing an extraordinary didactic exercise on the cutting-edge advances of respiratory medicine. Impressive progress has been made in the past 15 years, with new treatments available to manage and prevent airway infections. It remains to be seen how this might affect the related conditions of wheezing and asthma in predisposed and sensitised subjects. However, early data suggest that lower respiratory infection rates may reduce the development of the above conditions which are closely related to viral infections. Immunomodulators that both prime the immune system to fight infection and reduce inflammation are likely to play a major role in secondary and even potentially primary prevention of atopic diseases.

ANTIMICROBIAL RESISTANCE: A WORLDWIDE THREAT

The global antimicrobial resistance (AMR) crisis continues to increase in severity. The persistent worsening of the situation in recent years lends a pessimistic perspective to any summary of the state of play. Yet, through this perspective we may gain clarity, allowing the medical community to attack the problem with new ideas and strategies.

There are few better illustrations of the radically altered landscape of infectious disease care than comparing a case study from the beginning of the antibiotic era with another from the present day. In a seminal paper, Abraham et al.[1] reported the case of a 4-year-old child who was among the first patients in the world to be treated with penicillin. The patient presented with cavernous sinus thrombosis, secondary to pyoderma of the eyelids, a typical post-measles complication, caused by a bacterial superinfection by *Staphylococcus aureus*. The infection was refractory to sulfapyridine therapy and, upon admission, the child was semi-comatose, incontinent of urine and faeces, with gross oedema of both eyelids, bilateral proptosis, complete bilateral external ophthalmoplegia, and neck rigidity. He had meningoencephalitis due

to the massive staphylococcal infection. Following intravenous (IV) penicillin treatment the child improved rapidly and after 2 weeks his cerebrospinal fluid had become sterile.[1]

Sixty-seven years later, a 70-year-old man developed mitral endocarditis with a vancomycin-resistant *Enterococcus faecium* infection following a Whipple procedure to treat a pancreatic tumour. He displayed persistent bacteraemia after 12 days of treatment with linezolid. Therapy was changed to daptomycin (6 mg/kg/48 hours) with no effect; on Day 17 daptomycin dose was increased to 8 mg/kg/48 hours and doxycycline and gentamicin were added. Ten days later blood cultures remained *E. faecium*-positive (daptomycin minimum inhibitory concentration [MIC]: 2 mg/L). Therapy was changed to quinupristin/dalfopristin (MIC: 0.5 mg/L); however, the patient died on Day 33 of treatment with positive blood cultures.[2] Such severe cases of bacterial infection, resistant to all available antimicrobials, can now been found in hospitals across the world.

In 1992, the USA infectious disease specialist Harold Neu, published a paper warning of complacency regarding the threat of AMR.[3] Neu pointed out that many bacterial species were now resistant to the vast majority of older antibiotics. He highlighted the overuse of antibiotics, both in hospitals and the wider community, as the source of the problem and called for antibiotic control programmes, improved hygiene, and research to synthesise new agents in order to reduce further resistance and to avert a global AMR crisis. Twenty-five years later, despite the publication of hundreds of research papers on the subject and numerous national initiatives, society has failed to wean itself from irresponsible use of antibiotics and the crisis predicted by Neu has come to fruition. Recently, however, the gravity of the threat has begun to condense local initiatives into global action.

The World Health Organization's (WHO) 2014 global report on AMR[4] is the first attempt to create a worldwide perspective on AMR surveillance. The report identified substantial gaps in surveillance, characterised AMR as a threat to the achievements of modern medicine as a whole, and predicted the arrival of the post-antibiotic era if a significant change in direction is not achieved. The WHO has called for governments to improve surveillance, to allow a full understanding of the extent of AMR as a first step towards tackling the issue. The report stated: "A post-antibiotic era – in which common infections and minor injuries can kill – far from being an apocalyptic fantasy, is instead a very real possibility for the 21st Century."[4] This statement is starkly illustrated by the detection of both *Escherichia coli* resistant to third-generation cephalosporins or fluoroquinolones and methicillin-resistant *Staphylococcus aureus* (MRSA) in five of the WHO's six world regions (the Americas, Europe, Africa, the Eastern Mediterranean, South East Asia, and the Western Pacific) and multiple-drug resistant (MDR) *Klebsiella pneumoniae* in all world regions.[4]

A major UK government publication predicted a rise in deaths attributable to AMR from a low estimate of 700,000/year in 2014 to a potential 10 million/year in 2050, if the resistance crisis is not managed; these statistics indicate that AMR-related deaths would eclipse those caused by cancer. This number may appear dramatic, but it is in fact based on resistance of only three organisms (*K. pneumonia*, *E. coli*, and *S. aureus*) suggesting it is a very conservative estimate of the likely impact of unchecked resistance.[5]

THE EPIDEMIOLOGY OF RESISTANT ORGANISMS

AMR can be found in virtually all known forms of micro-organisms including viruses (*Varicella zoster* [chicken pox/shingles]), protozoa (*Plasmodium* sp. [malaria]), fungi, and bacteria. The most important factor determining AMR is the exposure of an organism to the selection pressure of an antimicrobial compound. The current state of AMR has seen MDR move from the hospital to the community, and community-acquired infections by MDR micro-organisms can now be found all over the world.

Focussing on bacterial species, the major organisms of concern in hospitalised patients are MDR *pneumococci*, MRSA, and vancomycin-resistant *enterococci*, among Gram-positives. Among Gram-negative bacteria, *bacilli* expressing extended spectrum β-lactamases (ESBL), carbapenem-resistant *Klebsiella* sp. and other enterobacteriaceae, MDR *Pseudomonas aeruginosa*, and MDR *Acinetobacter baumannii* are of most concern. Gram-negative *bacilli* represent the organisms of greatest concern due to their battery of defence mechanisms against antimicrobial compounds. MDR Gram-negatives are now found in the community and in animal hosts, causing serious

community-acquired as well as hospital infections. The first pan-resistant organisms are members of this group, and are discussed later.

Streptococcus pneumoniae is the major primary pathogen of community-acquired respiratory tract infections (RTI). In a 2014 study from Seoul, South Korea, five strains of pneumococcus were identified which were only susceptible to those antibiotics reserved for highly resistant infections (linezolid, tigecycline, and vancomycin).[6] In Mexico, a gradual erosion in the susceptibility of *S. pneumoniae* to the macrolide class of antibiotics is evident in comparisons of 2005–2007 data with that from 2008–2012. This group of antimicrobials is particularly important for paediatricians and the current prevalence of resistance (30–40%) precludes their use as an empiric therapy in Mexico.[7]

Enterococci, most commonly *Enterococcus faecalis*, are becoming increasing prevalent as hospital-acquired infections. In Europe, 90% of *E. faecalis* isolates are susceptible to vancomycin; however, in Canada, Latin America, and the USA, respective resistance prevalences of 22%, 28%, and 79% have been detected.[8]

MRSA represents >25% of *S. aureus* isolates found in the majority of southern European countries (Figure 1). The majority of central and northern European countries have >10% MRSA prevalence, with lower resistance generally restricted to Scandinavian countries and the Netherlands.[9]

Enterobacteria, in particular *E. coli*, are the most common Gram-negative bacteria encountered in hospitals. Antibiotic selection pressure has driven the evolution of hydrolysing β-lactamase enzymes creating ESBL capable of destroying cephalosporins and carbapenems. The worldwide prevalence of ESBL-producing *E. coli* has been increasing over the last decade, with the highest levels observed in the Asian and Pacific regions (28%) and Latin America (23%), according to 2009–2010 figures.[10] In *K. pneumoniae*, ESBL-producer prevalence has shown a similar upward trend, with 2008–2010 figures breaching 50% within Latin America (53%).[10] In the USA, national ESBL-producer prevalence was 12% in a study examining four species of enterobacteriaceae; however, there was significant regional variation with prevalence as high as 23% in the mid-Atlantic region and as low as 4% in the west-north-central region. Additionally, many of the strains expressed more than one gene for ESBL-production conferring multiple resistance pathways.[11] Hundreds of β-lactamase variants are now present worldwide, and human carriage of ESBL-producing organisms is increasing globally.[12]

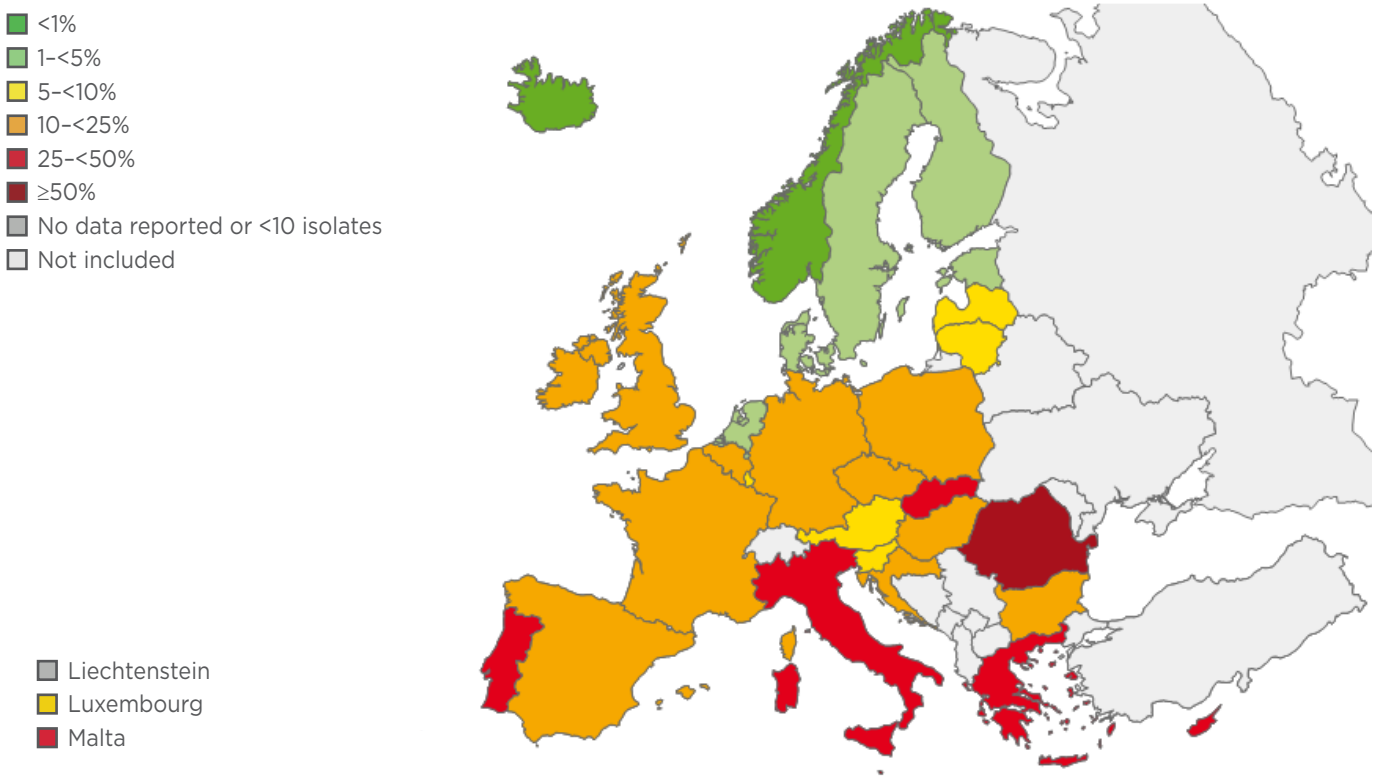

Figure 1: Proportion of MRSA isolates in participating countries in 2013.[9]
MRSA: methicillin-resistant *Staphylococcus aureus*

Despite their relatively protected status, carbapenems have been used liberally in immunosuppressed patients worldwide. In some European countries, such as Italy and Greece, carbapenemase-producing enterobacteriaceae are endemic. Even in the Netherlands which has extremely strict use of antimicrobials and search and destroy programmes targeting resistant organisms, ESBL-resistance cannot be avoided. Data indicate that single hospital outbreaks of carbapenemase-producing enterobacteriaceae have occurred; based on current trends, the situation is likely to worsen.[13]

Plasmid-mediated colistin resistance (MCR-1) represents the latest emerging threat. The polymixin colistin has been on the market since the 1960s, but has been avoided due to toxicity and poor penetration. Nevertheless, it remains highly active against Gram-negative bacteria and has become the last resort antibiotic against many MDR infections. The extent to which the *mcr-1* gene has disseminated among enterobacteriaceae remains to be determined; however, two cases of bacteraemia caused by *E. coli* producing MCR-1 have been reported in Switzerland. Neither patient had received previous treatment with polymyxins, travelled abroad in the past few years, nor had exposure to farm animals. These data suggest a silent, horizontal spread of the *mcr-1* gene plasmid in community-acquired *E. coli*, with the potential for disastrous consequences.[14]

In many minds, tuberculosis is an infection associated with the 19th rather than 21st century, yet MDR-tuberculosis, resistant to isoniazid or rifampin, is likely present in every country in the world. Furthermore, many countries have now had at least one case of extensively drug-resistant tuberculosis, which has few treatment options, with poor surveillance likely to be a cause of widespread under-reporting.[4]

ANTIBIOTIC CONSUMPTION

AMR is an elegant example of natural selection at work. Random mutations conferring resistance are advantageous for bacteria exposed to the selection pressure of naturally produced antimicrobials in the environment. However, this natural selection has been rapidly accelerated by the profligate use of antibiotics during the 20th century. Excessive use is not limited to medicine, it is a major issue in meat production, leading to direct resistance as well as downstream consumption by humans. Inappropriate use extends beyond use in non-bacterial infections, to inadequate dosing or treatment durations which favour survival of resistant bacteria.

Antimicrobial use is common outside human medicine, in fact approximately 80% of the annual use of antimicrobials in the USA occurs in livestock, agriculture, and aquaculture.[15] China uses more antibiotics than any other country; a 2007 survey estimated that 210 million kg of antibiotics were used, totalling >46% of these drugs used in farming.[16] China, alongside India, is the top consumer of antimicrobials and, therefore, the top producer of MDR organisms. Data on ESBL-producing *E. coli* in the faeces of hens, pigs, and cattle from Hong Kong shows a steady rise in all three species. In 2013, 70–80% of pigs and hens, and approximately 45% of cows tested had resistant gut flora.[17] There are no studies illustrating these relationships directly; however, there is an intuitive understanding of the relationship between the consumption of antimicrobial-treated animal products and AMR in humans.

Globally, consumption of antimicrobials rose by 40% between 2000–2010; however, this pattern hides a varied picture of reduced consumption in some countries and large increases in others. Annual consumption varies by a factor of ten across all middle and high-income countries. The economies of Brazil, Russia, India, and China, along with South Africa, were responsible for the vast majority of the growth from 2000–2010.[18]

The relationship between direct human antimicrobial consumption and AMR has been shown in Europe, where a surveillance system exists. A large range of consumption exists from approximately 10 defined daily dose per 1,000 inhabitants per day in countries such as Estonia and the Netherlands, and close to 40 defined daily dose per 1,000 inhabitants per day in Greece.[19,20] The countries consuming high amounts of antibiotics, such as Greece and Italy, unsurprisingly, tend to have the highest prevalence of resistance.

RESISTANCE IN *PNEUMOCOCCI*

We define a micro-organism's resistance to a specific antimicrobial based on the MIC, the lowest concentration that visibly inhibits bacterial growth overnight. MIC are subject to change overtime, and are calculated and released by specific organisations in Europe, including the European Society of Clinical Microbiology and Infectious

Diseases (ESCMID), and the Clinical and Laboratory Standards Institute (CSLI) in the USA.

S. pneumoniae is the most common cause of bacterially acquired RTI. In Mexico, the susceptibility of *S. pneumoniae* to the antibiotics tested decreased when comparing 2005–2007 and 2008–2012 data from the large T.E.S.T trial.[7] In many cases, when a bacterial strain develops resistance to a single antibiotic within a class, for example through β-lactamase production, the mechanism will confer resistance to all antibiotics within this class.

Common treatment options for community-acquired RTI include trimethoprim-sulfamethoxazole, tetracyclines, chloramphenicol, macrolides/azalides/ketolides, β-lactams, and fluoroquinolones. The macrolides, β-lactams and fluoroquinolones are perhaps the most commonly utilised and the consequent resistance mechanisms are well understood.

S. pneumoniae: Macrolide Resistance

Macrolides have been available since the 1950s, and have been frequently used against pneumococci, particularly in the paediatric population due to their safety and efficacy profile. Macrolides are protein synthesis inhibitors, targeting both peptidyltransferase and ribosomal translation. Hence, the macrolide must achieve a cytoplasmic concentration sufficient to have an effect, and pneumococci can become resistant by expressing efflux pumps (*mefA* or *mefE* genes) to extrude the antibiotic. A second, more complex and efficient resistance mechanism involves ribosomal methylase (*ermB* or, rarely, the *ermA* gene), which dimethylates pneumococcal 23S ribosomal RNA, preventing access to the antibiotic binding site. Other mutations that affect macrolide binding related to ribosomal proteins L4 and L22 have been described.

Pneumococcal infections have demonstrated the ability to acquire resistance *in vivo*. A 2002 published letter offers a tragic example of treatment-emergent macrolide resistance. A 28-year-old man presented with a 5-day history of cough and dyspnoea; sputum culture revealed *S. pneumoniae* infection. Treatment with 500 mg/day IV of azithromycin was initiated and the patient responded well; however, at Day 4 he began displaying progressive respiratory insufficiency and was transferred to intensive care. Despite administration of ceftriaxone and vancomycin, the patient progressed to multi-organ failure and died. Isolates of the *S. pneumoniae* taken after the patient's deterioration, displayed the same genetic markers (BOX typing patterns) as the initial culture, indicating it was the same strain. However, while initial isolates showed full susceptibility to all antibiotics tested, including penicillin, the second isolate had become resistant to erythromycin, azithromycin, and quinupristin/dalfopristin. Sequencing revealed that resistance was conferred by a mutation of the ribosomal protein L22.[21]

Such cases are not isolated. In northern Africa, trachoma is an endemic and a major cause of sight loss during childhood. The WHO conducts programmes in the region aimed at preventing trachoma via a single dose of azithromycin. During one such programme in Morocco, a 2.5-month-old infant with nasopharyngeal carriage of *S. pneumoniae* (serotype 22F) developed resistance after a single dose of the macrolide. In this case, resistance was conferred by a 23S ribosomal RNA 2059A>G mutation resulting in a MIC change from 0.5 mg/L pre-mutation to >256 mg/L post-mutation.[22]

Macrolide resistance is increasing worldwide, and is often associated with penicillin resistance. Two recent studies indicate that *in vitro* resistance, at any level, is a predictor of treatment failure. The development of treatment-emergent resistance is not an isolated event; therefore, care must be taken when prescribing a single macrolide to patients with extrameningeal pneumococcal infections. The prevalence of resistance will dictate the need to reassess current recommendations for the treatment of community-acquired infection.

S. pneumoniae: β-lactam Resistance

S. pneumoniae is a resident of the nasopharynx found exclusively in humans. The bacterium acquires its β-lactam resistance via transformation of foreign genetic material from other streptococci. The transfer of genetic material to the genes coding for penicillin binding proteins, reduces their binding affinity for the β-lactams, thereby decreasing the activity of these compounds. Unlike other resistance mechanisms, such as acquisition of a hydrolysing enzyme, changes in penicillin binding proteins confer gradual increases in resistance as the antibiotic's ability to bind and block bacterial-wall formation is degraded by gradually acquired genetic changes.

With no animal reservoir, eradication of *S. pneumoniae* would seem to be a possibility.

However, the existence of 93 *S. pneumoniae* serotypes, its ability to transit rapidly between individuals, and its capacity to confer AMR via gene transformation make *S. pneumoniae* an extremely adaptable organism. These features make areas of high-density human interaction, such as daycare centres, into factories for AMR with children swapping serotypes and bacteria, in turn, trading in resistance genes.

β-lactams act in a time-dependent fashion. The major pharmacokinetic/pharmacodynamic parameter which predicts eradication is the time that the concentration of the antibiotic in serum is above the MIC. Hence, dosing intervals are more important than increased dose in improving eradication. For example, during the standardisation of amoxicillin/clavulanate therapy increases in amoxicillin dose from 500 mg to 875 mg resulted in an increase in the time above the MIC from 36% to 44%, while a change from twice-daily to three-times-daily dosing increased the time above MIC from 36% to 55%.

The choice of β-lactam antibiotic is also an important consideration, particularly in the paediatric population. Among the oral cephalosporins, cefuroxime and cefpodoxime have the greatest activity against penicillin-susceptible *S. pneumoniae*. However, they have MIC that are 1–4 dilutions higher than amoxicillin against non-susceptible strains and cause more collateral damage than penicillins. As a result, when treating a pneumococcal respiratory infection orally, amoxicillin remains the β-lactam with the best pharmacokinetic and pharmacodynamic relationship, particularly in children, and the lowest impact on the resident flora. The oral cephalosporins, cefixime, cefaclor, ceftibuten, and loracarbef, and macrolides generally are not recommended because of the decreased activity of these agents against non-susceptible pneumococci.[23-25]

Even in penicillin-resistant strains, adequate dosing of the correct β-lactam remains an effective therapy. There have been no documented treatment failures with adequate dosing of penicillins or third-generation cephalosporins in patients with extrameningeal infections.[26] There is no evidence of increased mortality in penicillin-resistant pneumonia when adjusted for severity of disease and comorbidity. However, increased mortality is reported in meningitis caused by penicillin non-susceptible strains.

S. pneumoniae: Fluoroquinolone Resistance

Fluoroquinolones became part of the pneumococci treatment arsenal in the 1980s with the introduction of the relatively inactive ciprofloxacin. A large number of potential subsequent fluoroquinolone compounds failed due to toxicity concerns. However, those currently licenced, including levofloxacin and moxifloxacin, have excellent activity against pneumococcus.

The target of fluoroquinolones are the enzymes DNA gyrase and topoisomerase IV, which control the winding and unwinding of the bacterial genome required for replication. Pneumococci have several resistance mechanisms against fluoroquinolones, the most common involve mutations in genes encoding the target enzymes. Mutations frequently occur in *parC*, which encodes the A subunit of DNA topoisomerase IV, or *gyrA*, which encodes the A subunit of DNA gyrase. Less frequently, mutations can be found in the genes *parE* and *gyrB*, encoding the B subunits of these proteins. Efflux pumps also play a role in decreasing susceptibility, though these are less significant in conferring resistance. Acquisition of both *parC* and *gyrA* mutations confers complete fluoroquinolone resistance.[27,28]

The possibility of *S. pneumoniae* strains possessing an occult resistance mechanism, due to the presence of either a *parC* or *gyrA* mutation, creates potential issues for fluoroquinolone therapy. Indeed, as with macrolide therapy, there are well-documented examples of treatment-emergent resistance during fluoroquinolone therapy.[29-32] In all currently documented cases, the *parC* or *gyrA* paring has been detected and infections have displayed a staggering level of resistance to fluoroquinolone therapy.

Treatment-emergent resistance is more common in immunocompromised patients, due to reduced immune response, increased length of carriage, and increased density of organisms. Patients with myeloma, for example, may have greater bacterial diversity than otherwise healthy patients with pneumonia. Patients with structural lung disease are also at increased risk of treatment-emergent fluoroquinolone resistance.

Given the risk of occult single-gene mutations, it may be prudent to avoid the use of fluoroquinolone monotherapy in patients treated with fluoroquinolones during previous months. Furthermore, in patients with severe documented

pneumococcal infection, caused by strains with levofloxacin MIC ≥1 µg/mL, fluoroquinolones should be avoided or used in combination.[29,30,32,33]

STAPHYLOCOCCUS AUREUS

MRSA is perhaps the best-known MDR strain. Methicillin was the first synthetic β-lactam synthesised in response to penicillin resistance in 1959. A year later, the first MRSA isolates were cultured in UK laboratories. Hospital-acquired MRSA infection was detected in Western Europe, the USA, and Australia in the following decade. By the 1980s MRSA was making headlines outside the medical community and community-acquired MRSA had been documented. The end of the 1990s saw the first appearance of vancomycin-resistant MRSA;[34] now, MRSA represents a global community and hospital epidemic. In the T.E.S.T survey, the prevalence of MRSA in Mexico was 45%.[7]

The treatment of MRSA infections has traditionally relied on glycopeptides, mainly vancomycin; however, there has been a progressive erosion of the MIC of vancomycin, and alternative therapies are becoming important. Daptomycin is the best-known alternative, but has some limitations including being inadequate for pulmonary infections due to neutralisation by pulmonary surfactant, and bacteria infecting other locations beginning to show decreased susceptibility. Linezolid is another useful antibiotic in patients with serious MRSA infections that cannot be treated with glycopeptides; however, bone marrow toxicity limits its use and plasmid-mediated resistance represents a potential future threat.

Outcomes for methicillin-sensitive *S. aureus*, treated with vancomycin, are significantly worse than for MRSA infections.[35] Other issues with vancomycin therapy include poor tissue penetration, a slow bactericidal activity, difficulty in optimising dose, MIC creep, and the emergence of strains with varying levels of vancomycin susceptibility, including heteroresistant *S. aureus*, intermediate-level resistant *S. aureus*, and vancomycin-resistant *S. aureus*.[36] Some new agents for MDR Gram-positive cocci, such as MRSA, include two highly active lipoglycopeptides, oritavancin, and dalbavancin, oxazolidinone tedizolid, and two new cephalosporin β-lactams ceftobiprole and ceftaroline.

GRAM-NEGATIVE BACTERIA

Gram-negative bacteria are more complex than their Gram-positive counterparts and have an extraordinary capacity for defence and plasticity against antimicrobial compounds. Mechanisms include loss of porins, which reduces the penetration of some antibiotics though the cell membrane, conferring resistance to β-lactams such as imipenem; production of β-lactamases which hydrolyse antibiotics in the periplasmic space; over-expression of transmembrane efflux pumps, which target β-lactams, quinolones, aminoglycosides, tetracycline antibiotics, and chloramphenicol; metabolic bypass mechanisms, usually through a new enzyme bypassing the pathway inhibited by the antibiotic; ribosomal mutation or modification which impedes the binding of some tetracycline and aminoglycoside antibiotics; target-site mutations affecting the quinolones by altering DNA gyrase and topoisomerase IV; and enzymes that directly modify and inactivate antibiotics like aminoglycosides and ciprofloxacin.[37] Antibiotic selection pressure has driven the incidence of mutations, leading to resistance mechanisms following the introduction of each new class of antibiotic from ampicillin in the 1960s (*TEM*, *SHV* serine, β-lactamases), the cephalosporins in the 1980s (AcrAB, *blaSHV*, *blaTEM*, *AmpC*-type, β-lactamases), and carbapenems from the 1990–2000s (CTX-M-15, *VIM*, *IMP*, *NDM-1*, KPC, *OXA-48*, Porin defects) (Table 1).[38-41]

The β-lactamases of enterobacteriaceae, such as *E. coli*, have been evolving for more than 50 years. Four classes of β-lactamases are recognised: Class A, which can confer resistance to many β-lactams through the production of ESBL and carbapenemases, such as the *K. pneumoniae* carbapenemases that have become widespread in many parts of the world; Class B, metallo-β-lactamases, which are carbapenemases; Class C, cephalosporinases; and Class D, oxacillinases.

The terminology used to describe resistance has been evolving to keep pace with the extent of the resistance crisis. Researchers and physicians have reclassified organisms from resistant, to MDR, to extensively drug-resistant and, finally, to pan drug-resistant, for those bacteria with resistance to all licenced antimicrobials.[42]

Severe *E. coli* infections before the antibiotic era would be susceptible to 13 classes of antibiotic

available today. The emergence of the ESBL-producing enteric bacteria, following selection by those same antibiotics, leaves only four parenteral treatment options in high resistance areas (tigecycline, carbapenems, amikacin, and colistin), most of which represent a single antibiotic rather than a class; however, all these options have limitations. Plasmid-mediated resistance to polymyxins like colistin is the latest threat and toxicity of aminoglycosides has further reduced the number of available antibiotics to combat resistant organisms. This has resulted in increased use of carbapenems with the inevitable consequence of a progressive rise in resistance to these agents.

Carbapenemases are now emerging in various forms within Gram-negative bacteria. *K. pneumoniae* carbapenemases may be found not only in *K. pneumoniae* but also other enteric bacteria. Metallo-β-lactamases are produced by both *P. aeruginosa* and enterics. Oxacillinases capable of inactivating carbapenems are also emerging, both in *Acinetobacter*, and in both *K. pneumoniae* and *E. coli*.

COMBATTING ANTIMICROBIAL RESISTANCE

Little progress has been made in tackling resistance since the predictions of Harold Neu, some 25 years ago. Improved surveillance and the development of improved diagnostic tests are necessary to begin to address increased AMR. Molecular diagnostic testing creating a single point-of-care blood test to identify bacterial versus viral infections will help in rationalising antibiotic use. Pressure from an increasingly aware public, and consequently increased political pressure, is leading to more robust efforts against the spread of MDR bacteria and attempts to slow the emergence of resistance through improved antibiotic stewardship. Key to both these approaches is the prevention of infection. The increased understanding of AMR outside the medical community is accelerating research into new drugs through increased collaboration between drug companies, government, and non-profit organisations. Similarly, improved global co-ordination supported by organisations, such as the WHO, will help to combat highly mobile resistant pathogens.[43]

APPROPRIATE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA: LESSONS FROM A CASE STUDY

A 78-year-old woman was admitted to hospital. She had been symptom-free the previous evening before the rapid onset of chills, fever (oral temperature: 39.5°C), right-sided pleuritic chest pain, mild non-productive cough, and dyspnoea associated with minimal physical exertion. The patient had a history of rheumatoid arthritis, treated with prednisone (5 mg/day) during the previous 3 months; mild hypertension controlled with hydrochlorothiazide; and hospitalisation for acute pyelonephritis 2 months previously, during which she received fluoroquinolone treatment. She was living alone at the time of hospitalisation.

Physical examination revealed the patient was lucid and responsive. She displayed tachypnea (respiration rate: 35/min), tachycardia (pulse rate: 120/min), and her blood pressure was 130/85 mmHg.

Table 1: Gram-negative resistance mechanisms.

Class	*E. coli* and *K. pneumoniae*	*P. aeruginosa*	*Acinetobacter*	*B. fragilis*
Cephalosporins	ESBL, AmpC, KPC, MBL, OXA-48	AmpC, (ESBL), MBL	AmpC, (ESBL), MBL	NA
Carbapenems	KPC, MBL, OXA-48, porin loss	MBL, porin loss, efflux	OXA-23, -24, -58, MBL, porin loss, efflux	MBL
Aminoglycosides	AME, 16S methylases	AME, 16S methylases, efflux	AME, 16S methylases, efflux	NA
Fluoroquinolones	QRDR, efflux, PMQR	QRDR, efflux	QRDR, efflux, PMQR	NA
Metronidazole	NA	NA	NA	nim

AME: aminoglycoside modifying enzymes; *B. fragilis: Bacteroides fragilis; E. coli: Escherichia coli*; ESBL: extended spectrum β-lactamase; *K. pneumoniae*: *Klebsiella pneumoniae*; KPC: K. pneumoniae carbapenemase; MBL: metallo β-lactamase; NA: not available; *P. aeruginosa*: *Pseudomonas aeruginosa*; PMQR: plasmid-mediated quinolone resistance; QRDR: quinolone resistance-determining region.

The patient appeared hydrated with no peripheral adenopathy. Pulmonary examination revealed signs of consolidation and crackling rales in the right hemithorax. Heart rhythm was regular with no murmurs. There were no signs of jugular engorgement or peripheral oedema. Her abdomen was soft and without organomegalies; her neurological exam was normal.

Subsequent chest X-ray showed a well-defined infiltrate typical of pneumonia. The extent of the infection, also assessed by computed tomography scan, was large enough to touch the pleura, explaining the pleuritic chest pain.

Diagnostic Lessons

Chest X-ray is the essential diagnostic tool for acute pneumonia. As well as confirming the diagnosis, it may indicate the presence of complications (effusion, abscess, tumour, etc.), provide possible evidence of aetiology, and allow tracking of disease progress.

Along with chest X-ray, blood cultures are the second essential diagnostic tool, though not in the immediate phase due to the delay in receiving results. Blood cultures confirming bacterial infection are almost exclusively positive for pneumococcus in patients without risk factors for Gram-negative bacillus infection. In those with risk factors, *E. coli* is the second most common micro-organism found. However, other pathogens must also be considered. The abrupt onset and early signs of consolidation in the patient suggest that *Legionella pneumophila* is an unlikely candidate. An opportunistic infection, such as *Pneumocystis jiroveci*, is improbable due to the sharply defined radiological fissure ('ground glass' presentation is more typical), unilaterality, and low doses of prednisone which would be unlikely to cause significant immunosuppression.

S. pneumoniae is the most likely candidate micro-organism. The patient's age, recent hospitalisation, and pretreatment with a fluoroquinolone (ciprofloxacin), should alert physicians to the possibility of a MDR pneumococcal infection. Turning to Gram-negative bacillus the likelihood of *E. coli* infection is increased by the presence of risk factors including female gender, age, and recent hospitalisation.

Treatment Lessons

The patient's age, per se, is not a risk factor for a complicated disease course. However, the combination of age and comorbidities with possible immunosuppression do represent risk factors for a complicated course and unusual aetiologies of community-acquired pneumonia. In addition, tachypnea is a serious physical sign of prognostic importance.

Acute pneumonia requires empirical antibiotic therapy. Azithromycin is a poor choice of antibiotic in this case as pneumococcal infections are frequently resistant to macrolides and azithromycin is not active against Gram-negative infections, which remain a possibility in this case. Amoxicillin has little effect against most Gram-negative bacteria of interest in community-acquired pneumonia. Ceftriaxone is a serious consideration, because the resistance of pneumococci to the cephalosporins is very low, and ceftriaxone is also active in the majority of Gram-negative bacteria of interest in the community-acquired pneumonia. However, it does not cover *Legionella*, or other 'atypical' organisms. A fluoroquinolone would be a good choice if the previous treatment with ciprofloxacin and resultant risk of treatment-emergent resistance in pneumococci did not contraindicate its empirical use. Combined ceftriaxone-azithromycin therapy is the best choice for empiric treatment of serious community-acquired pneumonia as it covers the vast majority of potential pathogens. This combination has been shown more effective than monotherapy with a β-lactam in some patients with pneumococcal pneumonia.

Treatment Response

The patient received the combination of IV ceftriaxone-azithromycin, and after 48 hours showed improvement, with a temperature of 37.8°C and a reduced feeling of pain. Blood culture results revealed *S. pneumoniae* with intermediate resistance to penicillin (MIC: 1 mg/L). The results allowed the attending physicians to simplify the treatment, changing to an oral route and choosing a classical antibiotic in order to reduce costs.

Switching to an oral schedule is desirable when the patient shows a substantial improvement as it reduces the risk of catheter infection and venous thrombosis, as well as facilitating a move to ambulatory care. In this case, monotherapy with amoxicillin was feasible because the degree of resistance to penicillin is easily overcome with the appropriate dose (1 gram/every 8 hours).

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IMMUNOMODULATION: BASIC CONCEPTS AND CLINICAL APPLICATION

A narrative summary of selected presentations that took place on 11th–12th May 2017, as part of the Encuentro Latinoamericano de Infecciones Respiratorias Recurrentes (ELAIR) educational event in Mexico City, Mexico

Speaker

José Antonio Ortega Martell

Autonomous University of Hidalgo State, Pachuca, Mexico

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MEETING SUMMARY

The third Encuentro Latinoamericano de Infecciones Respiratorias Recurrentes (ELAIR) took place in Mexico City, Mexico, on 11th–12th May 2017. ELAIR brought together experts from across Latin America and further afield, continuing an extraordinary didactic exercise on the cutting-edge advances of respiratory medicine. Impressive progress has been made in the past 15 years, with new treatments available to manage and prevent airway infections. It remains to be seen how this might affect the related conditions of wheezing and asthma in predisposed and sensitised subjects. However, early data suggest that lower respiratory infection rates may reduce the development of the above conditions which are closely related to viral infections. Immunomodulators that both prime the immune system to fight infection and reduce inflammation are likely to play a major role in secondary and even potentially primary prevention of atopic diseases.

BASIC CONCEPTS IN IMMUNE SYSTEM FUNCTION

Immune System Development

Like other organ systems, such as the circulatory or respiratory system, the immune system is essential for human life. The organs of the immune system manage our interaction with the environment, forming protective barriers where necessary, and provide both active and passive defence against potential attackers.

The complexity of the human immune system reflects an evolutionary arms race of adaptation and counter adaptation which began up to 4 billion years ago with the simple biochemical defences of unicellular organisms. The key ability of self or non-self-recognition was developed in multicellular sponges and corals around 1.5 billion years ago; later, in prevertebrate coelomates present 600 million years ago, specialised cell cavities produced specifically adapted cells, among them immune cells capable of phagocytosis, a strategy used previously for feeding in unicellular organisms. In the same era, antimicrobial peptides (AMP) and pattern recognition receptions (PRR), which improved non-self-recognition, emerged. Four hundred million years ago, major histocompatibility complex (MHC) polymorphisms allowed a great leap forward in immune specificity, paving the road for adaptive immunity and the development of antigen-specific immunoglobulins (Ig) in reptiles. Finally, Ig diversified into role-specific subtypes, with the current Ig subtypes appearing

in mammalian species approximately 200 million years ago.

The species-level evolution of the immune system driven by genetic changes is reflected in a microcosm by the ontogenic evolution of each person's individual immunity. Ontogenic immune maturation occurs through epigenetic changes both *in utero* and throughout life. Indeed, even before fertilisation, sperm utilise potent immune-tolerising strategies to evade the female immune system and allow zygote formation; the mother's immune system must likewise develop tolerance mechanisms to the alloantigens in the resulting zygote and fetus. During and after birth, the baby will be exposed to a host of antigens over a rapid period, the nature of which will affect immune-system maturation. Mode of birth, namely vaginal versus caesarean, changes the exposure to microbiota, thereby modifying the immune system; the immune system is also influenced by the baby's developing microbiome which, in turn, has a strong influence on immune system development.[1] In addition to the well-known direct effect of colostrum on immunity in the newborn, breastfeeding also modifies the baby's microbiota. Breastfed babies have a more diverse gut microbiome, which in turn aids both immune development and homeostasis. This homeostatic effect of the gut microbiome continues throughout life, making maintenance of diversity and avoidance of deleterious factors, such as excessive antibiotic use, an important factor in maintaining a healthy immune system.

Epigenetic changes continue during childhood with the immune system reaching its functional peak in young adults. Following maturation, the major function-altering events in the immune system include the aforementioned reproductive immunotolerance and immunosenescence, the latter defined as the ageing process of the immune system. Immunosenescence increases the risk of infection and loss of control of inflammatory processes, which may predispose to heart disease, stroke, and Alzheimer's disease, as well as some forms of neoplasia. In addition, autoimmunity increases with age, resulting in an additional risk of disorders such as rheumatoid arthritis, myasthenia gravis, and diabetes. To put this risk into context, the lifetime risks of cancer and autoimmune disease in developed countries are estimated at 30% and 10%, respectively.

Structure and Function of the Immune System

While infection control is a key immune system function, it is not its sole purpose; the repair of tissue and disposal of damaged or neoplastic cells are also fundamental roles of the immune system. Supporting the development of the gut microbiome, which in turn supports proper immune function, is a further crucial task. These disparate roles are interdependent, as illustrated by the repair of tissue following immune-related inflammation or the removal of cells infected by viruses, and the harmonious activity of these roles is central to proper immune function. Like many organs and systems, the overriding function of the immune system is adapting to maintain homeostasis in a constantly fluctuating environment. This adaptive imperative is likely to be the reason behind the conservation of the manifold immunological strategies developed during the evolutionary process.

Discussion of immunity often focusses on innate and adaptive responses, missing the equally important constitutive immunity. Constitutive immunity is stimulus-independent, consisting mainly of barriers, while innate and adaptive immunity are stimulus-dependent responses. The innate system is characterised by a fast but non-specific response, while the adaptive system acts more slowly but with a specific and more efficacious response that confers long-term immunity. Constitutive immunity includes epithelial barriers such as the skin, mucociliary transport, natural AMP, and antimicrobial enzymes like lysozyme. Innate immunity comprises innate lymphoid cells (ILC), complement, mast cells, neutrophils, eosinophils, and basophils. The major effectors of the adaptive immune system are the multiple T and B lymphocyte subtypes, the latter of which produce Ig. As with immune system functions, the classes of immunity are interdependent and overlapping. Innate and adaptive immunity must function in unison with different detector and effector cells working in concert and harmony, similar to musicians in a cellular symphony. Some cell types cross over, with dual roles in both modes of immunity.

Constitutive Immunity

The tight junctions between cells of the body's various epithelial barriers protect against passage of viruses, bacteria, fungi, and allergens. The production of mucus by goblet cells and

the co-ordinated movement of cilia facilitate the mucociliary transport system, further impeding the entry of pathogens and allergens and aiding in their expulsion. Sufficient humidity, correct temperature, and proper viscosity of the mucus are all key factors for the function of the mucociliary transport system.

AMP are anti-infective proteins produced at the constitutive barriers and are active against both Gram-positive and Gram-negative bacteria; in addition, AMP can attack the viral envelope, fungi, protozoa, and even cancer cells. AMP also have an immunomodulatory role, producing a chemotactic effect, helping to reduce inflammatory response and aid its resolution, and interacting with and moderating the adaptive immune response. AMP also help to regulate the microbiota and function by two principal mechanisms: the formation of transmembrane pores, which has a cytolytic effect, and the penetration of the cell membrane and disruption of essential processes through binding intracellular molecules.

Innate Immunity

Activation of PRR is a primary stage in initiating the innate immune response. There are several types of PRR; however, externally expressed toll-like receptors (TLR) are one of the most important types. TLR recognise products known as pathogen-associated molecular patterns (PAMP) and begin a rapid response. Following activation, internal signal transduction cascades involving MyD88 and Trif lead to proinflammatory cytokine release. These cytokines then activate neutrophils and macrophages which clear the pathogens.

Activated neutrophils will move to the pathogen via chemotactic mechanisms before adhering to, endocytosing, and digesting the pathogen via the process of phagocytosis. Neutrophils also combat infections through the release of antimicrobial compounds via a process known as degranulation. The final antimicrobial tactic of neutrophils is the release of neutrophil extracellular traps (NET). These NET comprise webs of DNA which contain antimicrobial products and trap microbes, forming a physical barrier, particularly in the blood. The NET can either be released while the neutrophil continues to function or upon cell death by lysis in a controlled form of apoptosis, known as NETosis. The NET released by the sacrifice of neutrophils not only trap pathogens and toxins, but also promote their disposal and tissue repair. In comparison, macrophages are simpler cells, depending on phagocytosis to trap micro-organisms before merging their prison-like phagosomes with lysosomes, creating phagolysosomes where the micro-organisms are digested. However, even these simpler cells have other metabolic roles within innate immunity.

Natural killer (NK) cells actively monitor cells, checking for a ubiquitous molecule alongside the MHC Class I molecule and killing all cells that lack this molecular 'off' switch. Both viral infection and neoplastic processes may result in the loss of MHC Class I. NK cells form the ILC-1 cell group, alongside ILC-2 cells that help control extracellular pathogens and ILC-3 cells that have roles in inflammation, antimicrobial defence against fungus and bacteria, and tissue homeostasis. The ILC lie close to epithelial barriers and appear to have a role in maintaining barrier function; dysfunction of ILC has been linked to allergic conditions associated with the epithelium, such as asthma or psoriasis.

ILC are phylogenically and functionally related to cells of the adaptive immune system, sharing the same precursor cells and roles in fighting infection. T helper (Th)2 cells are functionally related to the ILC-2 group, Th22 and Th17 are related to the ILC-3 group, and Th1 cells are related to the ILC-1 group, which also contains NK cells. The feature that differentiates the innate and adaptive cells is the expression of antigen-specific receptors by Th cell groups.

Adaptive Immune System

The two major classes of effector cell in the adaptive immune system are the T and B lymphocytes. T cells mount a relatively rapid specific cytotoxic response, while B cells proliferate and produce Ig to target infection. T cell activation begins with dendritic cells, a type of specialised macrophage that presents antigens alongside MHC Class II and costimulation molecules. The antigen presenting dendritic cells first phagocytose pathogens before coupling their antigens to MHC II. T cells, which recognise the antigen, are then activated, triggering an adaptive response.

Due to their antigen specificity, naïve T cells spend many hours moving within and between lymph nodes, scanning dendritic cells and searching for their antigenic ligand.[2] Cytotoxic T cells activated by dendritic cells directly target virus-infected or neoplastic cells, while activated Th cells recruit and attract additional lymphocytes by releasing cytokines. The initial rapid effector T cell response, which confers immediate protection, is followed by

a slower memory T cell response, which protects against attack by the same pathogen in the future.

Different types of Th cells release different cytokines and activate different downstream effector cells. Th1 cells recruit cytotoxic T cells, IgG-bearing B cells, and macrophages, principally defending against intracellular micro-organisms. In comparison, Th2 cells recruit eosinophils, mast cells, and B cells bearing IgG, IgA, and IgE, defending against extracellular pathogens, including parasites, and regulating the allergic response; the Th1 cytokine cascade inhibits Th2 activity and vice versa. Another important Th subtype is the Th17 cell, which plays a role in tissue inflammation, autoimmunity, and defence against extracellular pathogens.

Like the immune system, Th cells must remain in balance, and T regulatory (Treg) cells play an important role in maintaining this balance. When a specific immune response is mounted, one Th type may dominate the immune landscape to curb a particular form of infection, and Treg cells restore balance following resolution of the immune response. As well as controlling excessive activity, regulatory immune cells control the migration of effector cells from the lymphoid tissue to the mucosa, where defence against invading pathogens is finalised. Persistent imbalance in Th cell populations is associated with autoimmune disease.

B cells are the other major class of adaptive immune-effector cell, with a principal role of antibody production. The most common antibody response occurs through a T cell-dependent pathway, where B cells resident in the germinal centre of lymphoid follicles are activated by follicular Th cells. Activated B cells proliferate, often differentiating into plasma blasts that produce IgM for a rapid but weak affinity Ig response. The next step of the antibody response involves differentiation into long-lived plasma cells, rapid proliferation, and affinity maturation, which improves the affinity of the antibodies produced. At this stage, isotype switching of antibodies also occurs; for example, between IgM and IgG-type antibodies. Different Ig subtypes are functionally specialised; for example, IgE is specialised to defend against parasitic pathogens, while IgA acts at the mucosa where it is released and then binds to a secretory component allowing prolonged activity in the harsh proteolytic environment. Following the initial antibody response, memory B cells will be produced, conferring long-term immunity. It is important to note that the effector and memory stages of immunity are not limited to T and B lymphocytes. These stages are reflected in the regulatory cell classes that prevent excessive immune activity, with memory regulatory cells persisting long-term and awaiting activation by antigens alongside memory T and B cells.

Atopy and Allergy

Multiple predisposing factors result in an allergic response and genetic predisposition and epigenetic changes may both play a role. Diet, the microbiome, and environmental factors, such as pollution, are also likely to be involved. Dysfunction in the Treg environment may result in an imbalance in Th populations, which contribute to an allergic response. The genetic predisposition to produce IgE in response to common allergens is known as atopy. For allergy to occur, atopy must be combined with sensitisation by an allergen, which is then followed by hypersensitivity involving inadequate regulatory control of the response against the allergen. The final inflammatory stage of the allergic response is that recognised by patients as an allergic reaction, and involves the symptomatic presentation of allergic conditions such as atopic eczema, allergic rhinitis, and allergic asthma.

The Rationale for the Use of Immunomodulatory Prophylaxis in Daily Clinical Practice

Respiratory tract infections (RTI) have become a clinical priority due to the substantial associated societal and personal burden of disease.[3,4] Their effect is particularly grave in conjunction with serious chronic conditions, with over three quarters (78%) of exacerbations in chronic bronchitis and chronic obstructive pulmonary disease being due to RTI.[5] Treatment of RTI is principally directed at symptom relief, using agents such as non-steroidal anti-inflammatory drugs to control fever and inflammation; however, antibiotics may be used to directly combat the infection when bacteria are the causal agents.

Viruses cause >80% of RTI; however, patient and family pressure can often cause physicians and pharmacists to prescribe antibiotics when evidence of bacterial infection is lacking.[6,7] Such excessive use of antibiotics has contributed to antimicrobial resistance and, therefore, a global reduction in the use of antibiotics is an urgent priority. In this context, the use of prophylactic antibiotics should be limited to exceptional circumstances, such as in patients with primary immunodeficiency or failure of the immune system, for instance,

in HIV-infected patients. Antimicrobial resistance makes the need for prophylactic strategies more pressing. Preventive measures against RTI include education, medical or surgical interventions, and both non-specific and specific immunomodulation.

Prevention of Respiratory Tract Infection

Behavioural interventions may be effective in reducing infection rates through a focus on parental education, encouragement of breastfeeding, and the reduction of modifiable risk factors, such as smoking in high-risk adult populations.[8,9] Other modifiable risk factors that may be targeted in public health campaigns include exposure to pollutants, avoidance of overcrowding, and treatment of concomitant medical conditions.[10-13]

For certain pathological conditions, targeted medical interventions, such as vaccination, do have a role and are strongly recommended where available.[14-16] Unfortunately, vaccinations are not available for the majority of pathogens responsible for common RTI.[17] Surgical interventions, such as tonsillectomy, will likely continue to have a place in the prevention of specific recurrent infection, but this should continue to be a last-resort option.

Non-specific immunomodulation is a longstanding approach for the prevention of RTI and is now gaining increased prominence. The non-specific approach broadly reinforces the ability of the immune system to fight infection and various types of immunomodulators have been developed, including plant-derived substances, bacterial lysates, bacterial ribosomal preparations, thymic derivatives, synthetic peptides, and chemical substances.[18] The quality of evidence for immunomodulators varies significantly; for example, despite use since the 1920s, evidence for the clinical benefit of *Echinacea* in treatment of rhinosinusitis has yet to be demonstrated.[19] Data from the well-respected Cochrane collaboration indicates that immunomodulators based on extracts from bacteria that commonly cause RTI have the strongest evidence base.[20-23] In addition, bacterial lysate immunomodulators have been used in Europe for >30 years.

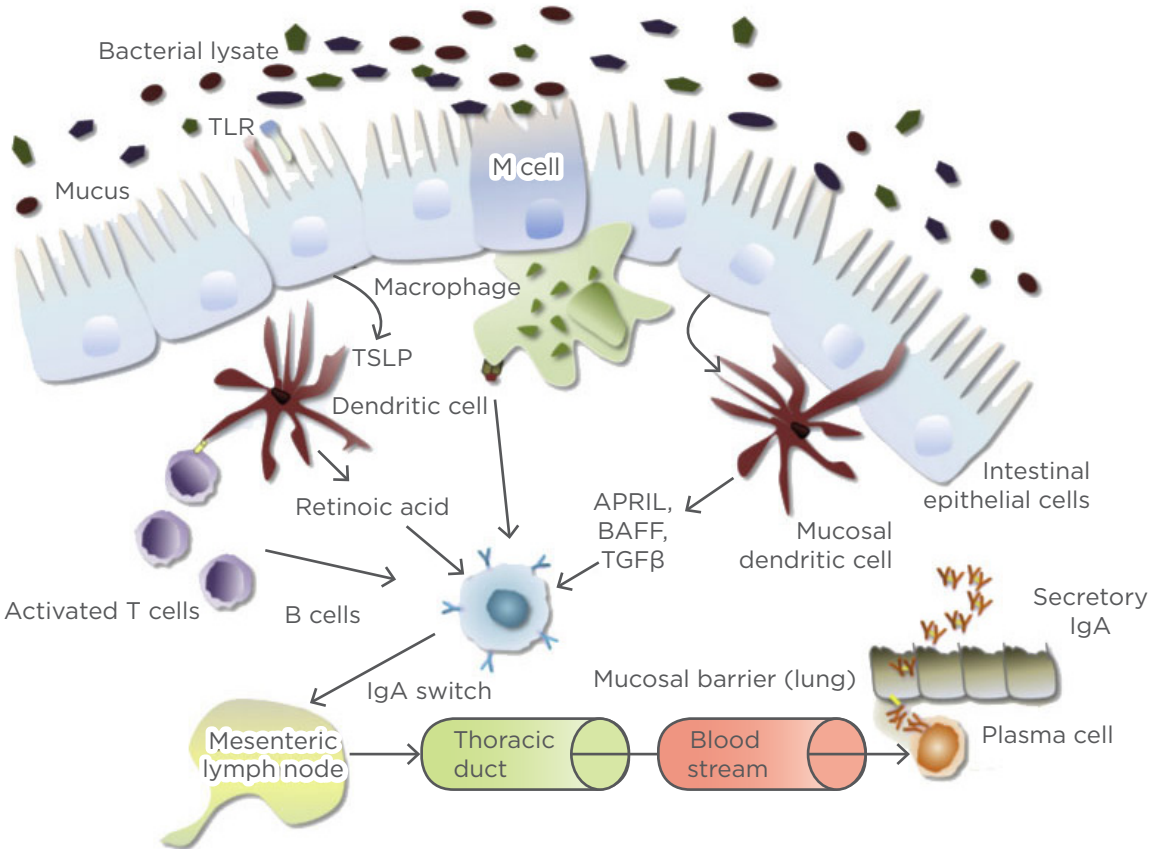

Figure 1: Immune system activation by oral bacterial lysates.
APRIL: a proliferation-inducing ligand; BAFF: B cell activating factor; IgA: immunoglobulin A; TGFβ: transforming growth factor beta; TLR: toll-like receptor; TSLP; thymic stromal lymphopoietin.
Adapted from Pfefferle et al.[24]

BACTERIAL IMMUNOMODULATORS: MODE OF ACTION

Bacterial lysates contain PAMP and other antigens capable of activating the innate and adaptive immune system (Figure 1). M cells located in the gut mucosa transport antigens to specialised antigen presenting dendritic cells and macrophages; dendritic cell processes also infiltrate the mucosal barrier, allowing direct trapping of antigens, and TLR expressed by gut epithelial cells may also be activated following oral administration of bacterial lysates.[24] As previously noted, dendritic cells are important for the activation of T lymphocytes, including Treg lymphocytes, which in turn activate B lymphocytes allowing the production of IgA, the key secretory Ig of the mucosal system (Figure 1).[24] In addition, the improved mucosal activity of secretory IgA is derived from the secretory component that protects the antibody from degradation by proteolytic enzymes in the mucosa. Following detection of bacterial-lysate derived PAMP, the common mucosal immune system allows the spread of these gut-derived immune activities to lymph nodes in the mesentery and the chest, distributing antimicrobial activity to other mucosa.[25]

Immunomodulation by bacterial lysates involves both induction of immune system effector cells and activation of immunoregulatory cell classes. This effect mirrors that of the commensal microbiota, which both stimulate immune system maturation and reduce allergic sensitisation. Bacterial lysate immunomodulators induce immune-effector cells, reducing infection, and activate immunoregulatory cells, reducing inflammation. Evidence from *in vitro*, *in vivo*, and human trials indicates that the immunomodulatory effects of bacterial lysates induce effector cells in both the innate and adaptive immune system and their respective regulatory dendritic cell and regulatory T and B cell populations.[26] Much of the immunomodulatory response is dependent on the previously mentioned TLR, expressed on epithelial cells, dendritic cells, macrophages, monocytes, and T and B lymphocytes. The type of TLR that is activated determines the downstream activity; production of cytokines raises an inflammatory response against pathogens, chemokines attract cells to the site of infection, and regulatory cytokines, such as interleukin (IL)-10, help to control inflammation.[26]

The innate response involves synergistic activation of TLR-4, TLR-2/6, TLR-9, and TLR-7/8. TLR-4 and 9 are the most extensively studied and evidence suggests that TLR-9 may be active in immunoregulation. Chemokines CXCL-1, CXCL-6, and CXCL-8 attract neutrophils that help fight bacteria and the activation of cytotoxic ILC-1 group cells improves both antibacterial and antiviral responses. Proinflammatory and antiviral cytokines induced by immunomodulators such as OM-85 as part of the innate response include IL-1β, IL-6, and tumour necrosis factor α, and IL-12, interferon (IFN)-α, IFN-β, IFN-γ, respectively.[26]

Bacterial lysate immunomodulators also induce cytokines related to the adaptive immune system including the B cell-activating cytokines IL-10, B cell activating factor (BAFF), and IL-6. Activation of the adaptive Th and B cell classes by immunomodulators has been demonstrated, as has the Ig response cascade of rapid IgM production, followed by IgG and IgA. Alongside IgA, which is central to the mucosal immune response, IgG has the advantage of being more widely distributed and providing a longer humoral memory response.[26]

The immunoregulatory effects of bacterial lysate immunomodulators involve maturation of both plasmacytoid and myeloid dendritic cells, indicated by the presence of T cell regulatory proteins CD80 and CD86. Activation of CCR7 has been demonstrated and is key for the migration of dendritic cells to mesenteric lymph nodes and bacterial-lysate related activation of CD4+ CD25+ FOXP3+ Treg cells has also been verified *in vitro*. There are several subpopulations of these regulators, like Treg 1, that predominantly produce IL-10, and Th3 cells that produce transforming growth factor beta (TGF-β). IL-10 is very important for the production of antibodies and for the control of inflammation, while TGF-β is necessary for lymphocyte maturation and IgA production. Regulatory cell expression of the chemokine receptor CCR9, which helps cells to migrate towards the mucosas, is also increased by immunomodulators.[26,27]

Mechanistic Data for the Bacterial Lysate Immunomodulator OM-85

OM-85 is the best-studied of the bacterial lysate immunomodulators.[20] Data from Navarro et al.[27] demonstrates activation of dendritic cells in the intestinal mucosa by OM-85 leading to antigen presentation and maturation of T cells to Th2 cells in a mouse model. These Th2 cells support B cells in the production of secretory IgA, before

migration to the airway mucosa where they continue producing secretory IgA as well as TGF-β. Alongside the aforementioned functions, TGF-β aids tissue repair through activation of fibroblasts. The dual pro-immune/anti-inflammatory immunomodulator model is exemplified by the Type 1 regulatory T cell-related production of anti-inflammatory IL-10, induced by OM-85.[27] This mouse data has been replicated in chronic obstructive pulmonary disease patients, where OM-85 induced a synergistic increase in the production of IL-10 under proinflammatory conditions.[28] OM-85 also acts in a modulatory manner on molecular assemblages, known as inflammasomes, which are gaining increasing importance as key initiators of inflammation. Inflammasomes are sets of molecules that assemble inside the cell in response to infection, tissue damage, or metabolic imbalance, to activate the major inflammatory cytokines, IL-1β and IL-18, amongst others. Inflammasome assembly principally depends on three classes of molecules: a sensor molecule, an adaptor protein, and caspase 1. In the majority of currently described inflammasomes, the sensory molecules are nod-like receptors, a PRR related to TLR but located within the cytoplasm rather than on the cell surface. NOD-like receptors trigger inflammasome formation, where they assemble alongside adaptor proteins and pro-caspase 1; inflammasome formation results in pro-caspase 1 conversion to activated caspase-1. The subsequent protease activities of caspase-1 then result in fragmentation of the IL-1β and IL-18 precursors and their subsequent activation (Figure 2).

In a recent study, incubation of dendritic cells with OM-85 induced a pre-activated state in two inflammasomes important in viral airway disease, with no increase in pro-caspase levels. The authors suggested that this primed state may aid the inflammatory response following viral infection. In line with this hypothesis, production of antiviral IFN-β was also demonstrated in dendritic cells via OM-85-induced stimulation of the previously mentioned TLR Trif and MyD88. OM-85 also resulted in decreased release of inflammasome-dependent inflammatory cytokine IL-1β and reduced neutrophil, eosinophil, and macrophage activity, in a model of bacterial infection using challenge with lipopolysaccharide and the adjuvant alum.[30]

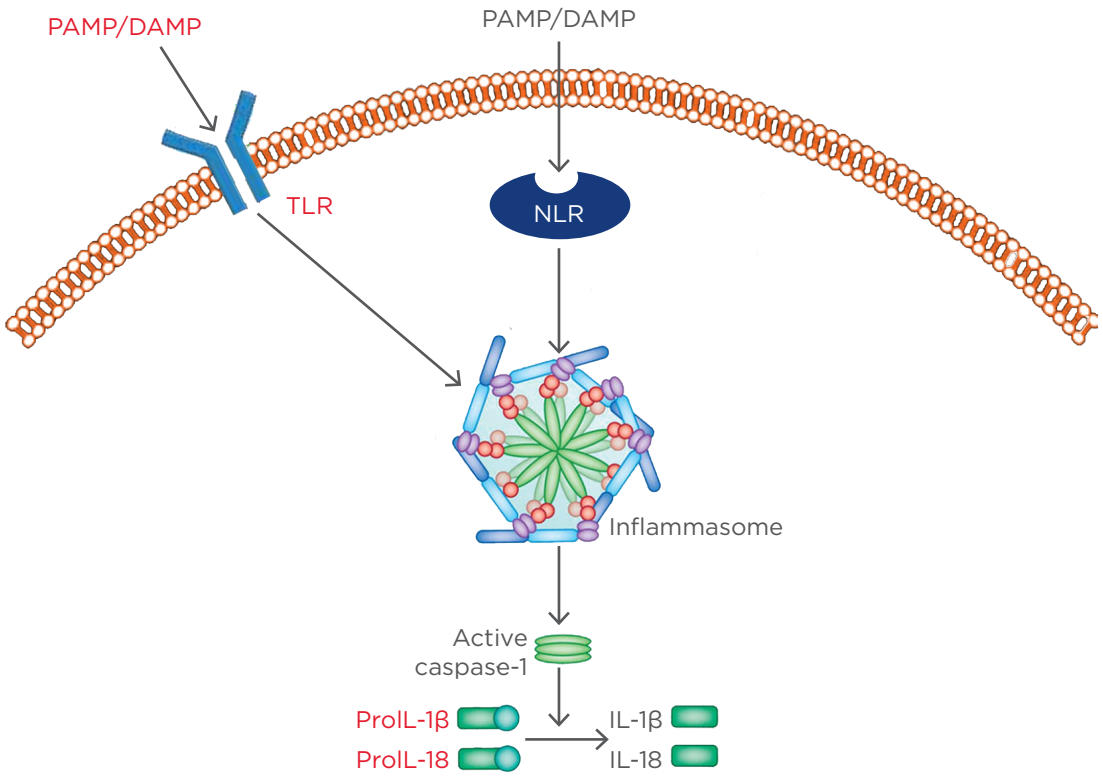

Figure 2: Inflammasome formation leads to the activation of inflammatory cytokines.
DAMP: damage-associated molecular patterns; IL: interleukin; PAMP: pathogen-associated molecular patterns; NLR: NOD-like receptor; TLR: toll-like receptor.
Adapted from Shao et al.[29]

CONCLUSION

The functional immune system protects against infection while maintaining homeostasis in a fluctuating environment. Mechanistic evidence suggests bacterial lysate immunomodulators, such as OM-85, support immune homeostasis and help fight infections via the induction of an immune response, creation of a pre-alert inflammatory state, and a concurrent reduction in inflammation.

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UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN AND ADULTS: BURDEN AND MANAGEMENT

A narrative summary of selected presentations that took place on 11th–12th May 2017, as part of the Encuentro Latinoamericano de Infecciones Respiratorias Recurrentes (ELAIR) educational event in Mexico City, Mexico

Speakers

Ricardo L. Marengo,[1] Alberto Ciceran,[2] Blanca E. Del Río Navarro[3]

1. University Institute CEMIC, Buenos Aires, Argentina
2. University of Buenos Aires, Buenos Aires, Argentina
3. Allergy department, Hospital Infantil de Mexico Federico Gomez, Mexico City, Mexico

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MEETING SUMMARY

The third Encuentro Latinoamericano de Infecciones Respiratorias Recurrentes (ELAIR) took place in Mexico City, Mexico, on 11th–12th May 2017. ELAIR brought together experts from across Latin America and further afield, continuing an extraordinary didactic exercise on the cutting-edge advances of respiratory medicine. Impressive progress has been made in the past 15 years, with new treatments available to manage and prevent airway infections. It remains to be seen how this might affect the related conditions of wheezing and asthma in predisposed and sensitised subjects. However, early data suggest that lower respiratory infection rates may reduce the development of the above conditions which are closely related to viral infections. Immunomodulators that both prime the immune system to fight infection and reduce inflammation are likely to play a major role in secondary and even potentially primary prevention of atopic diseases.

CHRONIC AND RECURRENT RESPIRATORY TRACT INFECTIONS IN ADULTS: DISEASE BURDEN

Upper respiratory tract infections (URTI) have a significant societal impact as leading causes of physician visits and work absenteeism in adults. In developed countries, acute respiratory tract infections (RTI) account for 20% of all medical consultations and 75% of all antibiotic prescriptions.[1] The economic burden of RTI is considerable, with figures from the year 2002 suggesting that >$2 billion was spent on over-the-counter medications in the USA, and the annual cost of acute URTI to the UK NHS was estimated at £60 million.[2]

Respiratory tract pathologies have the same names in childhood and adulthood, yet the presentation in the context of the developing versus fully developed respiratory and immune systems may be substantially different. Chronic rhinosinusitis (CRS) is a frequently encountered condition in adults and is defined as a persistence of sinus inflammation for >3 months. Symptoms include nasal obstruction, congestion, rhinorrhoea, anterior discharge, posterior drip, and facial pain. Secondary to these symptoms are headache, facial pressure, ear pain, halitosis, cough, dental pain, fever, and fatigue. Given their persistence, the impact on the quality of life (QoL) of a sufferer may be significant.

CRS affects approximately 11% of the population throughout Europe and 14% of the population in the USA.[3-6] Individuals with both acute disease and CRS consistently score below the general population in both physical and emotional aspects related to QoL, as assessed by the 36-Item Short Form Survey (SF-36) (Figure 1).[7,8] In light of the societal and personal impact, numerous evidence-based guidelines have been published to raise awareness within the clinical community and improve the diagnosis and management of rhinosinusitis and its subtypes.[3,4]

Those adults at a higher risk of URTI are collectively known as 'fragile adults'. Typical factors increasing the risk of URTI include an impaired immune response, which may be due to immune deficiency or other immunity-related issues, such as atopy. Environmental and behavioural risk factors include smoking and exposure to pollution.[9] Chronic respiratory disease also predisposes patients to acute infection due to physiological alterations.[10,11] In the elderly, impaired phagocytosis and the process of immunosenescence are known to increase this risk.[11]

The vast majority (90%) of RTI are caused by viruses. Misuse and overuse of antibiotics in the treatment of RTI, particularly in CRS, contribute to antimicrobial resistance. Antibiotics can also cause collateral damage by impairing the host microbiota, which creates a substrate for further infections. Beyond the impact on those individuals directly affected, antimicrobial resistance in respiratory disease also represents a risk for dissemination of resistant infection to the wider population. As a result, prophylactic antibiotic use for RTI is only appropriate in exceptional circumstances and decreased use of antibiotics is an urgent priority.[12-17]

Effective management of URTI is a priority due to the significant individual and broader socioeconomic impact.[18,19] The majority of treatment remains focussed on symptom relief using antipyretic and anti-inflammatory drugs because, in most cases, infections are viral and not amenable to antimicrobial therapy. Given these limited options, the focus of management should be weighted towards prevention rather than treatment. Behavioural interventions and targeted surgical treatment may be of use in adults, particularly fragile adults. The use of immunomodulators to bolster the defensive capacity of the immune system offers an additional prophylactic strategy available to adults suffering chronic URTI.[20]

RECURRENT RESPIRATORY TRACT INFECTIONS IN CHILDHOOD

Recurrent respiratory tract infections (RRTI) are very frequent in childhood and have the potential to be extremely severe. From the immunological perspective, children face a hostile world from the moment of birth, with threats represented in the form of antigens. Parental defence against this hostile environment extends to the immune system; however, at 6 months of age the passive immunity conferred by maternal immunoglobulins (Ig) expires, and immunological immaturity confers an environment where RRTI may exceed normality in terms of frequency and severity.

After reaching a nadir at approximately 6 months of age, when maternal IgG can no longer be absorbed due to gut closure, IgG levels steadily increase, reaching approximately 80% of adult levels by 5 years of age (Figure 2). However, the principal Ig for protection against respiratory immunity, IgA, only attains 40% of its adult levels by 5 years of age (Figure 2). As a result, immune immaturity is particularly marked in the respiratory system. Maturation of all aspects of the adaptive immune system is modulated by the innate immune system; this system also shows functional immaturity after birth and, in some infants, abnormalities in innate immunity will have downstream effects on adaptive immunity, further increasing the risk of RRTI. Alongside functional immune immaturity, the anatomical immaturity of the pulmonary system increases the risk of RRTI, which makes antigen-rich environments such as day care nurseries a significant challenge.

RRTI may occur in the upper airway (otitis media, mastoiditis, pharyngo-tonsillitis, adenoiditis, and rhinosinusitis) or the lower airway (bronchitis/bronchiolitis, tracheitis, and pneumonia). At times, infections may involve the entire airway, such as in the infectious processes of rhinovirus and influenza virus. URTI represent the majority (80–90%) of RTI;[21] RTI are often self-limiting and those that are not easily managed are usually lower respiratory tract infections (LRTI), which are more severe and difficult to treat.

A universally agreed definition of RRTI is currently lacking. Six or more URTI, or at least one infection per month during autumn and winter, in children >3 years of age, or eight or more episodes per year in children <3 years old, have been proposed as suitable definitions. For LRTI, the lower

rate of ≥3 episodes per year has been proposed. Both the aforementioned proposals relate to patients without immunological deficiency or functional/anatomical alterations. A more generalised concept of RRTI being present is when a child displays a higher frequency of infections compared to peers from the same age cohort and environment.

Twenty-five percent of the morbidity experienced by children due to RTI occurs during the first year of life, concurrent with the immunological nadir that accompanies gut closure to IgG. Another 18% of morbidity occurs in children aged 1–2 years, during which time the spike of antigen exposure due to attendance of nurseries generally occurs.

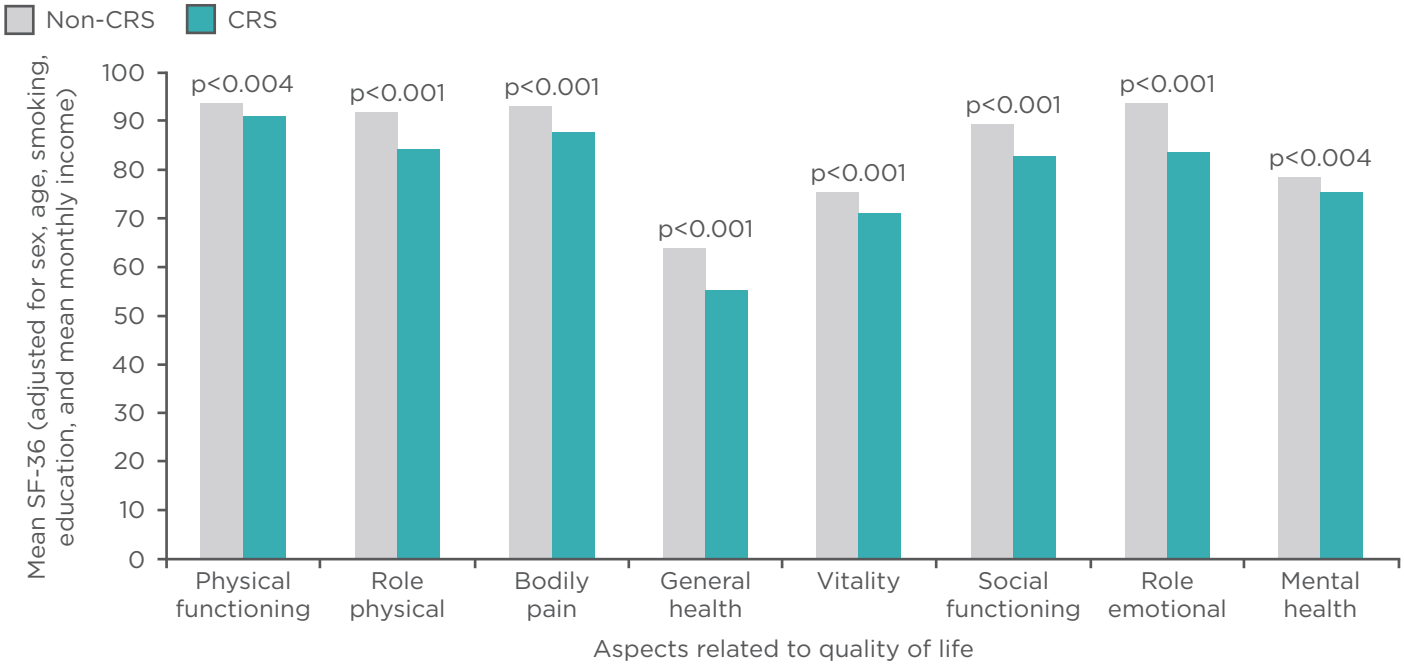

Figure 1: Impact of chronic rhinosinusitis on quality of life in a large Chinese population-based survey (N=1,411).

CRS: chronic rhinosinusitis; SF-36: 36-Item Short Form Survey.

Adapted from Fu et al.[7]

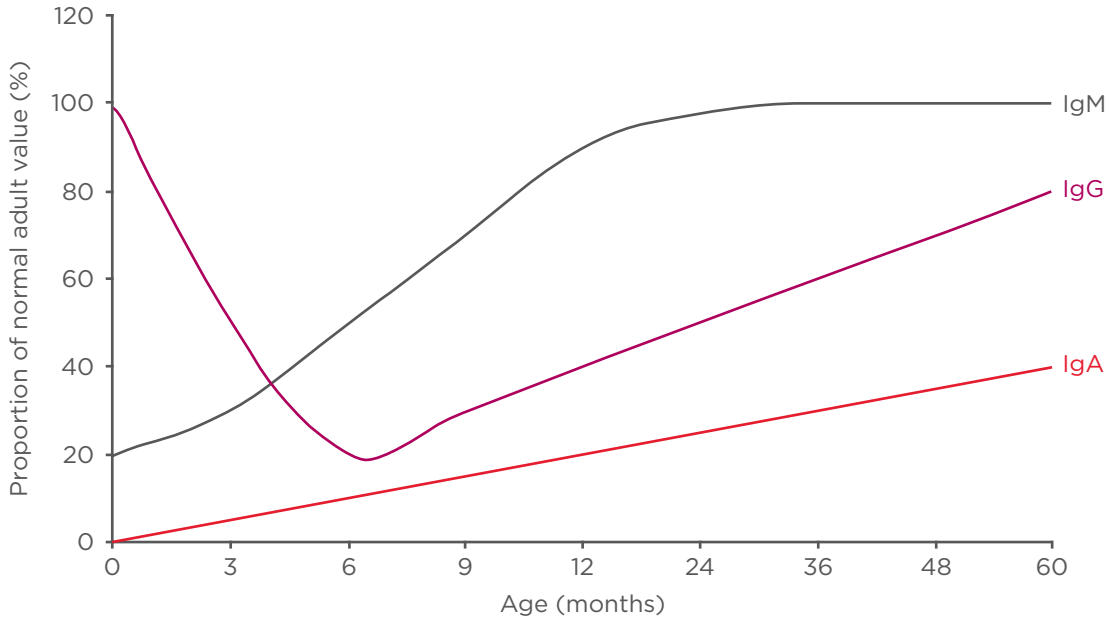

Figure 2: Immunoglobulin capacity as a proportion of adult values by age.

Ig: Immunoglobulin.

Furthermore, 19% of all child deaths from RTI occur within the first 5 years of life.[22,23]

Aetiology

The vast majority (90%) of RRTI are caused by viruses. Common causal agents include respiratory syncytial virus (RSV), rhinovirus, and viral influenza. The remaining 10% of infections involve bacteria but generally also have a viral element, manifesting as joint viral/bacterial superinfections. Bacterial causal agents include *Streptococcus pneumoniae, Haemophilus influenza, Staphylococcus aureus*, and *Klebsiella pneumoniae,* amongst others.

Previously, RSV was considered the most prevalent RTI pathogen during childhood. However, data from studies using molecular techniques such as the polymerase chain reaction indicate that rhinovirus is in fact the predominant pathogen.[24] Rhinovirus finds a permissive environment for replication in the adenoids following entry through the upper airway, and from this site can initiate both URTI and LRTI.

The functional immune immaturity of infants combines with multiple risk factors to precipitate respiratory infections, including overexposure to antigens in nurseries, allergies, siblings, seasonality, environment, and lack of breast feeding. A study in the Netherlands directly demonstrated the effect of targeting risk factors rather than the disease itself. Breast feeding for ≥6 months was associated with a reduced risk of LRTI in infants ≤4 years of age, compared with children who were never breastfed (adjusted odds ratio: 0.71; 95% confidence interval [CI]: 0.51–0.98).[25]

The burden of respiratory disease is borne both by the child and their family, leading to an overall economic burden, school and work absenteeism, misuse of antibiotics and associated resistance, decline in pulmonary function, and impact on QoL.[26] In a Chinese study, children aged 2–7 years affected by RRTI had significant deficits in physical, emotional, social, and school functioning ($p<0.05$).[27] LRTI are more serious and are associated with an increased risk of wheezing or asthma, hospitalisations, and death.[26] Hospitalisation with pneumonia is a serious condition in children and adolescents, with 21% of patients requiring intensive care. Approximately 50% of hospitalisations in this age group are caused by a single virus, with an additional 15% being caused by viral–viral coinfection. Similar patterns are seen in the <2 years age group (approximately 80% single and co-viral infections) and the 2–4 years age group (approximately 80% single and co-viral infections). More than half of children aged <2 years hospitalised due to pneumonia tested positive for RSV or rhinovirus, while just under half of those aged 2–4 years tested positive for RSV and/or rhinovirus.[27]

The predominance of viral rather than bacterial aetiology in RTI is most marked in preschool children, with 95% of infections being viral in this age group. In school age children, the proportion drops to approximately 85%, and in adults it is 80%. The high rate in preschool children is likely to be at least partially mediated by a Type 2 T helper (Th2) cell predominance in the functionally immature immune system. Th2 cells are involved in defence against parasites but have more limited activity against viruses. In addition, Th2 cells have a role in allergy. The combined effect of Th2 dominance and viral RRTI may lead to wheezing, which increases the risk of developing asthma. Furthermore, in a vicious cycle of sorts, in those patients who do develop asthma, RTI are a major trigger for exacerbations.[28-30] The extremely high predominance of viral infections in preschool children further underlines the need to avoid antibiotic use in this population unless absolutely necessary.

Recent data have shown that the nasopharyngeal microbiome, which is colonised during the first year, affects both the severity of LRTI and asthma.[31] Early colonisation of the nasopharynx was by *Staphylococcus* or *Corynebacterium*, followed by *Alloiococcus*; transient appearance of *Streptococcus*, *Moraxella*, or *Haemophilus* was associated with increased viral infections. The presence of these virus-associated bacteria was linked to inflammatory processes, an increased chance of LRTI, and an increased risk of wheezing or asthma. Antibiotic use was also associated with these pathogenic species, providing a possible mechanism behind the reported association between early antibiotic use and asthma.

CAN THE MANAGEMENT OF RECURRENT RESPIRATORY TRACT INFECTION AND CHRONIC RESPIRATORY DISEASES BE IMPROVED?

Knowledge and detection of risk factors is the first step in the prevention of RRTI. Education of parents, reduced exposure to environmental pollutants, active immunisation, and the use

of immunomodulators may all improve RRTI prevention.[32,33] Cochrane systematic reviews represent the gold standard for evidence-based medicine.[34] In 2012, an update on the first 2006 Cochrane review on immunostimulants for the prevention of RTI was published.[35,36] The goal of the analysis was to assess the safety and efficacy of immunostimulants administered to children as RTI prophylaxis therapy. Data from randomised trials on the use of immunostimulants and immunomodulators for the control of RTI in children ≤18 years of age were included. The primary outcome of interest was the number of acute respiratory infections during the period of analysis. Children with allergies, asthma, anatomical malformations, Down's syndrome, or other forms of immunodeficiency were excluded.[36]

Of the 764 studies identified, 61 studies were included, comprising 4,000 patients. Of the included studies, 45 lasted <6 months, 35 lasted 6 months, and 2 lasted >6 months. The included studies were evaluated for quality (Level A, B, or C) before data extraction. The extracted data revealed significant heterogeneity and variability in the trials. Immunostimulators were shown to reduce RTI (-1.24; 95% CI: -1.54–[-0.94]), with a difference in rates of -39% (95% CI: -46.37–[-31.31]). The overall quality of evidence for any immunostimulant versus placebo was moderate and depended on the number of URTI in the control group.[36]

Data from studies on bacteria-derived immunomodulators had the least heterogeneity and variability, particularly those studies investigating the effects of the bacterial lysate OM-85. Of the 12 OM-85 studies assessed, all were of ≥6 months' duration. Four OM-85 trials were the only A-rated studies amongst bacterial immunomodulators, with the remaining 8 OM-85 studies rated quality-level B. The reduction in the total number of acute respiratory tract infections as compared to placebo was 35.90% (95% CI: -49.46–[-22.35]).

OM-85 Prophylaxis in High-Risk Children

OM-85 prophylaxis was assessed in a 6-month study of children aged 3–5 years with a history of RRTI and subnormal IgG subclasses (N=54).[37] The frequency of subnormal IgG subclasses was high in this population (78%) and OM-85 significantly reduced the incidence of acute RTI by approximately 40%. A separate randomised double-blind trial investigated the use of OM-85 in the city of Chihuahua, Mexico, in children aged 1–12 years (N=54) with a history of RRTI. The study ran for 12 months and encompassed two 3-month dosing schedules of OM-85 at 3.5 mg/day for 10 days/month (standard dosing) or placebo. OM-85 prophylaxis resulted in a lower use of antibiotics from Month 2 onwards, including during the winter months when extreme weather was prevalent, which was mirrored by a reduction in the number of RTI.[38]

Overexposure to respiratory pathogens is common in orphanages. From the researcher's perspective, orphanages also have the advantage of providing a homogenous environment for study participants. A randomised double-blind placebo-controlled trial investigated the use of OM-85 in girls aged 6–13 years (N=200) living in an orphanage. Participants received either OM-85 prophylaxis at the aforementioned standard dose or placebo. During the 6-month follow-up, which encompassed the winter season, participants who received OM-85 had a 50% reduction in the incidence of RTI. All untreated children required antibiotic therapy, while approximately 50% of patients who received OM-85 prophylaxis also received antibiotics. The relative risk reduction increased along with increased frequency of RTI, with a risk reduction for ≥3 RTI of 0.2 versus placebo, indicating an 80% reduction in risk. As well as representing a reduction in the burden of illness for individuals, including reduced absences from school, these changes likely resulted in a significant cost saving for the institution.[39] Similarly, in an open-label multicentre study carried out in an orphanage, OM-85 decreased infections, the use of antibiotics, and school absenteeism when given in the acute phase of infection. In addition, OM-85 had an increased protective effect in those patients who had a history of more frequent infections.[40]

As with all medical interventions, safety of immunomodulators is a key consideration. Data from the 2012 Cochrane review show that OM-85 has a risk difference of close to zero compared with placebo (0.01; 95% CI: 0.01–0.03).[36] The documented adverse events were mild in nature and consisted of gastrointestinal events, including diarrhoea, or skin reactions.

Efficacy in Acute Respiratory Tract Infections

The aforementioned data, as well as similar studies such as by Chen et al.,[41] in children in remission from CRS, show that OM-85 has a prophylactic effect in RRTI. Though its primary role is in prophylaxis, open-label and controlled studies have shown that OM-85 accelerates the recovery of patients when used during the acute phase of the

infectious process. In a randomised double-blind trial in children aged from 18 months to 9 years (N=56) with subacute rhinosinusitis, therapy with OM-85 reduced convalescence (15.38±8.91 days versus 20.28±7.17 days) and promoted faster recovery (5.56±4.98 days versus 10±8.49 days) compared with placebo with these children.[42] Similar results showing both curative and prophylactic effects of OM-85 were found in another study on acute episodes of CRS in children.[43]

Immunogenicity

Vaccination is the primary preventative measure against viral infections. Safety, efficacy, and immunogenicity were investigated in a 6-month prospective, randomised, single-blind study in children (N=68) who received OM-85 in combination with inactivated influenza vaccine. Incidence, mean number, and prevalence of RTI were all significantly lower in children who received OM-85 prophylaxis compared with vaccine prophylaxis alone. Missed school days and the number of antibiotic courses were also significantly lower in the combined prophylaxis group. Furthermore, there was no difference in anti-inactivated influenza vaccine IgG and IgM, indicating that OM-85 did not interfere with the vaccineimmune response.[44]

IMMUNOMODULATORS IN RHINOSINUSITIS GUIDELINES

In the current European position paper on adults with rhinosinusitis, OM-85 prophylaxis in CRS without nasal polyps has an evidence level of 1B and recommendation grade A, the second highest evidence level, below only nasal steroids.[20] Pan-American guidelines state the beneficial effect of preparations of bacterial lysates in adults to reduce the proportion of recurrence in viral and bacterial rhinosinusitis, and that the benefits of bacterial lysates outweigh the risks. These guidelines also recommend bacterial lysate therapy for CRS without polyps, though sufficient evidence for CRS with polyps is lacking.[45] There are currently no guideline recommendations for the use of bacterial lysates in children. However, as detailed previously, data from diverse geographical regions and paediatric populations suggest a benefit, and Brazilian guidelines mention the benefit of bacterial lysate therapy in children with RRTI that may lead to CRS.[46]

CONCLUSION

Children and fragile adults are particularly vulnerable to the development of RRTI, as well as chronic conditions such as CRS. As the definition of recurrence varies, it can be a challenge for physicians to interpret research and choose the optimal therapeutic option for their patients. Treating each case as an individual, both from a pathological and patient-focussed standpoint, can help guide treatment. When assessing RRTI, risk factors should be taken into account, the importance of the URT microbiome should be considered, and rational and minimal use of antibiotic should be a key consideration. Given the downstream consequences of RRTI in terms of increased asthma risk, hospitalisation, morbidity, and mortality, appropriate prophylaxis remains a major unmet need. Behavioural interventions, targeted medical and surgical interventions, and non-specific immunostimulation or immunomodulation should all be considered in the context of individual patient circumstances. Immunomodulators should be a significant part of a physician's preventative strategy, alongside a proper medical diagnosis, environmental control, effective nutrition, and appropriate use of other medications. The bacterial lysate immunomodulator OM-85 has the most robust and consistent evidence base. In RRTI, OM-85 has been shown to reduce incidence, convalescence, and the use of antibiotics, as well as being more effective in children with risk factors, such as those who attend nurseries or live in orphanages. It has also proved to be tolerated and effective in combination with the influenza vaccine and to be able to speed recovery and decrease convalescence during the active management of rhinosinusitis.

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WHEEZING AND INFECTION-TRIGGERED ASTHMA EXACERBATION: IS PREVENTION IN EARLY CHILDHOOD POSSIBLE?

A narrative summary of selected presentations that took place on 11th–12th May 2017, as part of the Encuentro Latinoamericano de Infecciones Respiratorias Recurrentes (ELAIR) educational event in Mexico City, Mexico

Speakers

Manuel E. Soto-Martínez,[1] José Antonio Ortega Martell,[2] Marcus H. Jones[3]

1. Pediatric Pulmonologist, Hospital Nacional de Niños, Universidad de Costa Rica, San José, Costa Rica
2. Autonomous University of Hidalgo State, Pachuca, Mexico
3. Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil

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MEETING SUMMARY

The third Encuentro Latinoamericano de Infecciones Respiratorias Recurrentes (ELAIR) took place in Mexico City, Mexico, on 11th–12th May 2017. ELAIR brought together experts from across Latin America and further afield, continuing an extraordinary didactic exercise on the cutting-edge advances of respiratory medicine. Impressive progress has been made in the past 15 years, with new treatments available to manage and prevent airway infections. It remains to be seen how this might affect the related conditions of wheezing and asthma in predisposed and sensitised subjects. However, early data suggest that lower respiratory infection rates may reduce the development of the above conditions which are closely related to viral infections. Immunomodulators that both prime the immune system to fight infection and reduce inflammation are likely to play a major role in secondary and even potentially primary prevention of atopic diseases.

ASTHMA PATHOPHYSIOLOGY: ROLE OF RESPIRATORY TRACT INFECTIONS

Asthma is a major public health problem with a conservative global prevalence of 235 million people. The economic (>$18 billion annually in the USA) and humanitarian burden of asthma falls more heavily on developing countries, where management tends to be poorer, increasing the risk of exacerbations and their consequences, such as hospitalisations and absenteeism. In developed countries, more vulnerable members of society, such as children and minorities, are at higher risk from asthma.[1]

Asthma in Latin America

Latin America covers 13% of the Earth's terrestrial surface and is home to approximately 600 million people. Despite being viewed as a homogenous cultural block, the region is highly diverse with a great breadth of sociodemographic characteristics, multiple languages and religions, and health services with disparate structures and resources. There is currently poor knowledge concerning

asthma prevalence and precipitating factors within the region;[2] however, the data that do exist indicate that asthma is a significant health problem in Latin America. In the 2009 phase of the global International Study of Asthma and Allergies in Childhood (ISAAC), Latin American countries often fell within the highest prevalence category (≥20%).[3] In a recent systematic review, the prevalence ranged between 7% in Mexico and 33% in Peru (Figure 1).[2]

Natural History of Asthma and Wheezing

Severe asthma is associated with reduced quality of life, school and work absenteeism, and increased healthcare costs. Data from the longest running longitudinal cohort study on asthma, initiated in the 1970s, indicates that poor control in childhood translates into increased severity and morbidity in adulthood.[4-7] Debate exists regarding whether increased asthma prevalence reflects a true epidemiological shift or whether it is driven by improved detection. The weight of evidence, however, suggests that the true global prevalence is increasing. Knowledge of risk factors has improved substantially over recent decades, allowing researchers to explore whether increased exposure may explain the increased prevalence of asthma. Risk factors may be region specific; for example, pollution and diet in Eastern Europe and obesity and stress in developed Western countries. The diversity of Latin America means that the full range of global risk factors can be found within the region.[1,2]

Exposure to asthma risk factors may begin prenatally with tobacco smoke and maternal diet. Diverse postnatal sensitising factors include exposure to mites, smoking, pollution, ozone, infection, and vitamin D deficiency.[8] Latin American data suggest that societal factors, such as exposure to violence, may also increase asthma prevalence.[8-10]

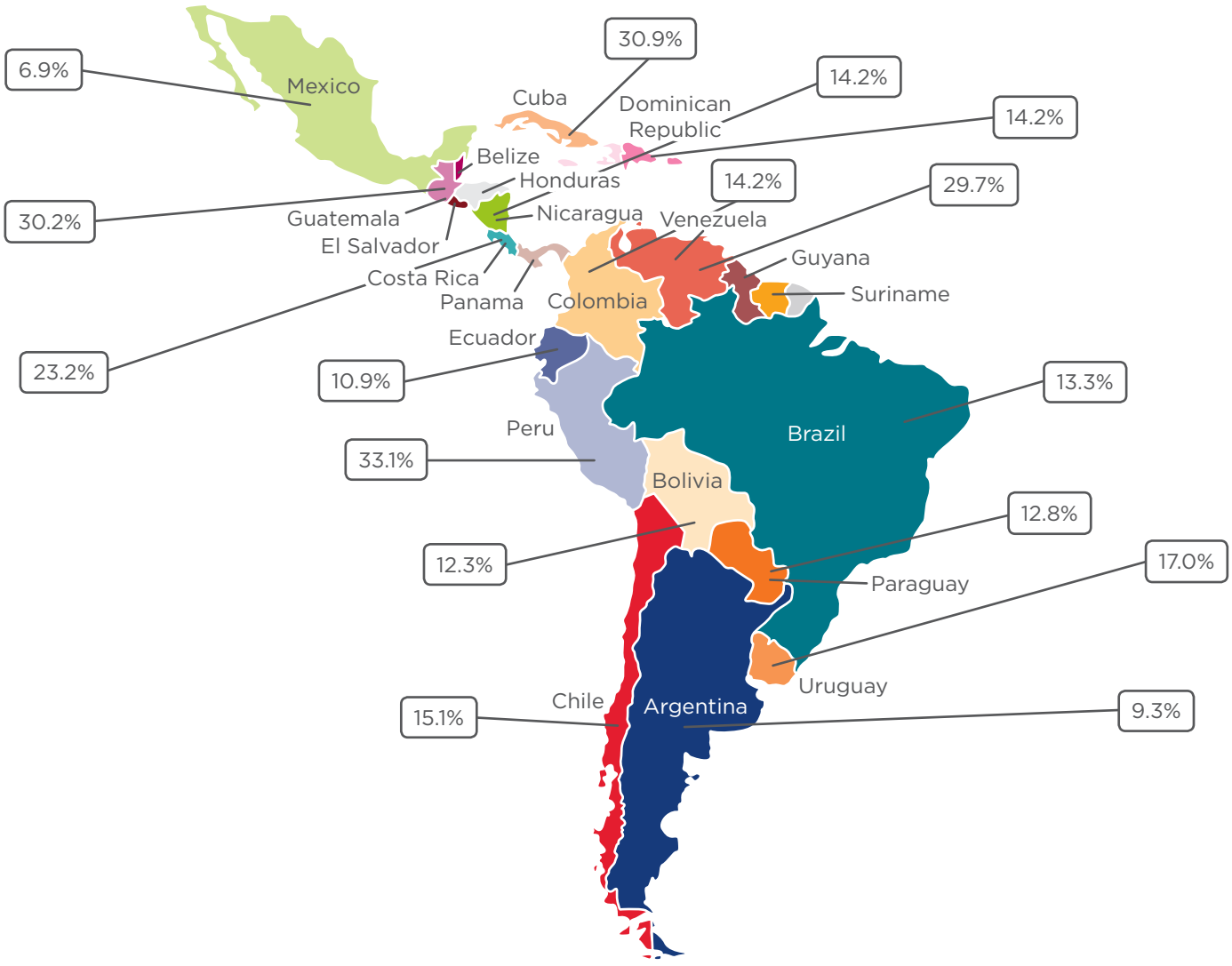

Figure 1: Asthma prevalence in Latin American countries.[2]

Perhaps the three principal predisposing factors, however, are genetics, pollution, and early exposure to viral infections. These widespread risk factors share a common consequence: increased proinflammatory changes, which are the basis of asthma pathophysiology.[8]

Definitions, Genetics, Phenotypes, and Pathophysiology

Asthma is no longer considered a disease, but rather as a heterogeneous group of conditions that result in recurrent, reversible bronchial obstruction, characterised by inflammation, hyperresponsiveness of the airway, and airflow limitation.[11,12] Defining a heterogeneous group of conditions poses a challenge. The classical definition of asthma characterises the condition in terms of recurrent episodes of shortness of breath, with cough and wheeze, occurring mainly at night. Using this definition, most patients have mild disease, risking under-diagnosis, under-treatment, and inadequate control. The physiological definition focusses on airflow limitation and the presence of inflammatory biomarkers. In Latin America, spirometry to detect airflow limitation is underutilised, particularly in children, and, in some cases, is not available. Finally, the pathological definition focusses on chronic inflammation, with or without airway changes, including remodelling.

A definition based on genotype is not simple, as >100 asthma-associated genes have been identified so far. Asthma also has multiple phenotypes, including episodic, exercise-induced, and atopy-induced asthma. Recently, definition via endotype, where disease subtype is classified by the distinct pathophysiological mechanism, has been proposed. The requirement to consider the influence of epigenetics on gene expression adds a further layer of complexity to this already multifactorial environment.

The wide range of heritability (35–95%) is in line with the multiple associated genes, endotypes, and mechanisms. Data suggest single nucleotide polymorphisms have a weak influence on asthma risk. Studies of common genetic variants suggest associations with viral infection or vitamin D deficiency mechanisms; however, so far, genetic studies have made little progress towards prognostic utility.[11] The Latin American population appears to share a large overlap of candidate genes with other populations, including transforming growth factor beta 1 (*TGF-β1*), 17q21 locus, interleukin (IL)-13, glutathione S-transferase Mu 1 (*GSTM1*), matrix metalloprotein (*MMP*) 9, and β2 adrenoceptor (*ADRβ2*). Genes associated with asthma severity, vitamin D and E deficiency, and obesity, such as thymic stromal lymphopoietin and *MMP12,* were first identified in Latin America. Epigenetic studies have also identified interactions between candidate genes related to IL-10, *TGF-β1*, and dust mite allergens, and the previously mentioned association with exposure to violence is associated with DNA methylation of the *ADCYAP1R1* gene.

The three classical phenotypes of transient early wheezers, non-atopic wheezers, and immunoglobulin (Ig)E-associated wheeze/asthma have been split into six pathophysiological wheezing endotypes, here presented in ascending order of wheeze persistence: never or infrequent, pre-school-onset remitting, mid-childhood-onset remitting, school age-onset persisting, late childhood-onset persisting, and continuous wheeze.[13,14] In a longitudinal cohort study, the prevalence of these phenotypes was 60.0%, 19.0%, 7.5%, 4.3%, 4.7%, and 4.9%, respectively.[14] The detailed characterisation of asthma into endotypes associated with features such as the extent of IgE and T helper (Th)2 involvement, relationship to obesity, IL-5 predominance, and relationships with steroid and β2 agonist response, poses a great challenge in the field.

Inflammatory processes, influenced by both genetics and environmental factors, are fundamental to the pathogenesis of asthma. More recent data suggest a central role for the airway epithelium in asthma. Pathogens, allergens, and pollutants activate innate signalling receptors in the airway epithelium, by pathogen-associated molecular patterns, damage-associated molecular patterns (also called alarmins), and allergens resulting in the release of three principal cytokines; IL-25, IL-33, and thymic stromal lymphopoietin.[15,16] The resulting production of Type 2 cytokines, particularly IL-4, IL-5, and IL-13, results in increased trafficking of immature antigen-presenting dendritic cells to the epithelium, and increased antigen processing. These dendritic cells then drive T cell differentiation, often favouring Th2 cells, and consequent inflammatory processes.[15]

Bronchial biopsies of asthma patients reveal significant airway inflammation characterised by the presence of eosinophils, lymphocytes, neutrophils, and mast cells. Structural changes including smooth muscle hypertrophy and epithelial

denudation also occur. Though still important, the previous position of eosinophils as the key asthma mediator has been superseded by the airway epithelium, particularly during exacerbations, and Th2 cells, which are definitive in determining whether asthma is atopic or non-atopic. The role of neutrophils and oxidative stress has also gained increased prominence in recent years.[17,18] The recently published Mexican asthma treatment guidelines[19] propose two main branches in the pathophysiology of asthma: the Th2/ILC2/NKT branch, which results in eosinophilic inflammation in an IgE-dependent (Th2) or independent (ILC2/NKT) fashion; and the Th1/ILC1/Th17/ILC3 branch, which drives neutrophilic inflammation via an interferon (INF)γ-dependent (Th1/ILC1) or an IL-17-dependent pathway (Th17/ILC3). Ultimately, both pathways result in the bronchospasm associated with asthma exacerbations.[19]

Tissue changes caused by asthma include infiltration of the above inflammatory cells, as well as mucus cell hyperplasia. Thickening of the subepithelial basement membrane increases in smooth muscle mass both through hypertrophy and hyperplasia, and the presence of mucous plugging are classical features of asthma.[20] The median onset of asthma is 3 years in males and 8 years in females; in males, 80–90% of cases occur before the age of 4 years.[21] Previously, airway remodelling was thought to take place only in chronic or severe cases, particularly in adults. We now know this is not the case, it occurs in children, and may be present regardless of level of severity. Data now suggest that pathological changes also begin at an early stage of disease. Increases in inflammatory cells and leukotrienes are evident in children aged <3 years with persistent wheezing.[22] Basement membrane thickening and eosinophil infiltration appear to take place between the ages of 1 and 3 years, though they are absent in younger infants with persistent wheeze.[23,24]

The Role of Infection

Microbes represent a dichotomy for asthma risk. A balanced microbiome is essential for the development of the immune system and avoidance of atopy, while infectious pathogens increase the risk of developing asthma and suffering exacerbations.[25]

Hospitalisation due to respiratory syncytial virus (RSV) or rhinovirus-associated bronchiolitis during infancy are strongly associated with the presence of allergy and asthma later in life.[26,27] Wheezing caused by rhinovirus during the first year of life is the strongest predictor of wheezing at 3 and 6 years of age, and severe RSV leading to wheezing in early life increased asthma prevalence to approximately 40% by 18 years of age, compared with 9% in controls.[26,28-30]

When comparing the two pathogens directly, wheezing related to rhinovirus (odds ratio [OR]: 9.8) in the first 3 years of life conferred significantly more risk of developing asthma by 6 years old than RSV only (OR: 2.5). Furthermore, the combination of rhinovirus and RSV (OR: 10.0) conferred only a marginally higher risk than rhinovirus alone. In total, 90% of children who experienced wheezing due to rhinovirus by 3 years of age had asthma at 6 years of age.[31] This pattern continues into adolescence, with wheezing caused by rhinovirus in the first 3 years increasing risk of asthma, adjusted for wheeze caused by other infections, up to the age of 13 years, at which point RSV no longer increased risk (OR: 1.0). Early infection (<1-year-old) with rhinovirus also results in a greater risk of asthma during the first 5 years of life.[32]

In a long-term prospective study of patients with severe RSV bronchiolitis (N=206), 73% of children exhibited wheezing at 3 years old and 30% of patients had a diagnosis of asthma at 5 years of age. At 13 years old, RSV causing severe bronchiolitis resulted in an OR of 9.3 for the development of asthma or recurrent wheezing.[29] In a Costa Rican study (unpublished data), similar patterns were observed. Children (N=172) hospitalised for bronchiolitis during the first year of life, 25% of whom were pre-term deliveries, were contacted at age 6–7 years. Almost 40% of the patients had been diagnosed with asthma, 73% had a history of wheeze, 3% had visited the emergency room (ER), and 50% had a history of nebulisation.

In a study investigating non-viral infections, hypopharyngeal bacterial colonisation in asymptomatic infants was associated with wheezing/asthma by age 5 years (OR: 4.5; 95% confidence interval [CI]: 2.18–9.57). In addition, the risk of hospitalisation was also higher for those colonised as neonates. Of the four bacteria investigated, the risk was increased for colonisation by *Streptococcus pneumoniae, Haemophilus influenza,* and *Moraxella catarrhalis,* but not *Staphylococcus aureus*.[33]

Prospective interventional data on palivizumab, a monoclonal antibody against RSV, further strengthen the causal link between viral infection and wheezing or asthma. Palivizumab is recommended for high-risk infants, such as premature babies, and has achieved an approximate 50% reduction in infection rates.[34] The multicentre, matched, double cohort study investigated palivizumab asthma prevalence in premature infants. Preterm infants who were treated with palivizumab during the previous season and not hospitalised for RSV during the following winter (n=191) were matched with two control groups with (n=76) or without (n=154) a documented RSV hospitalisation. Palivizumab therapy resulted in a reduction in the relative risk of recurrent wheezing through the ages of 2–5 years in patients with no family history of atopy (80% reduction) or asthma (68% reduction).[35] There was no reduction in patients with a family history of atopy, where patients are at a higher risk of developing asthma later in life. Similar randomised controlled trial results demonstrated a significant reduction in cumulative wheezing over the first 12 months of life in preterm infants treated with palivizumab.[36] An article supports these data, suggesting that palivizumab administration in pre-term infants suppressed recurrent wheezing during the first 6 years of life, however, it did not suppress the onset of atopic asthma. Thus, morbidity is reduced despite there being no prevention of asthma development.[37] These data are in line with the hypothesis that, in order to avoid the development of asthma, three arms of risk driven by allergy, viral infections, and the microbiome of the airways must be addressed, presenting a significant challenge for the healthcare system.[38]

The importance of the microbial environment in the development of asthma has been elegantly illustrated in two studies comparing asthma rates between children from the Amish and Hutterite communities. Though genetically very similar, exposure to endotoxins in dust was 6.8-times higher in Amish children, corresponding to a 4–6-times lower rate of sensitisation, compared with Hutterite children. Authors identified innate immune system exposure to a rich microbial environment as the source of the difference in allergy and asthma between the two communities.[39,40]

Asthma Diagnosis

Variability in the presentation of asthma and age-dependent changes in children's symptom patterns add an extra layer of complexity to asthma diagnosis. A good clinical history, with knowledge of family background, risk factors, and previous infections is key, as is a thorough physical examination and differential diagnosis to rule out other conditions, such as the presence of foreign bodies or cystic fibrosis, or comorbidities, such as allergic rhinitis, sinusitis, and gastro-oesophageal reflux.

Rapid and accurate diagnosis is particularly important in infant and pre-school children due to a high prevalence of wheezing and associated morbidity. In this age group, 48% of children have experienced an exacerbation in the previous 12 months. Infants and pre-school children have the most severe episodes of exacerbations due to viral triggers, with worse symptoms and more frequent hospitalisations.[41] However, heterogeneity, overlapping symptom profiles, and a lack of objective or practical measures make diagnosis particularly challenging. Common differential diagnoses include recurrent viral respiratory infections, gastro-oesophageal reflux, foreign body aspiration, bronchomalacia, cystic fibrosis, primary ciliary dyskinesia, and vascular ring, amongst others.

In children ≤5 years old, clinical history is fundamental as it can help determine if episodes are recurrent or persistent, or if they are related to exercise or triggered by exposure to environmental pollutants. These details may help diagnose the endotype of asthma present. Family history of allergic disease should be considered, particularly in first-degree relatives. Finally, clinical improvement during 2–3 months of treatment and worsening following withdrawal are indicative of asthma.

Treatment Guidelines

Multiple treatment guidelines for asthma exist, however, broadly their messages are in sync. The recently published Mexican asthma treatment guidelines integrate aspects of UK, Global Initiative for Asthma (GINA), Spanish, and Australian guidelines, adapting them from the highly varied regional nature of Mexico.[19] Goals include adequate control of the symptoms and exercise tolerance, reducing exacerbations, avoidance of side effects, and maintenance of normal lung function. Regional and cultural factors affect tactics for asthma treatment which should be tailored to individual patient needs, in relation to cultural or ethnic beliefs and practices. The goals of treatment remain the same regardless of the societal or economic factors.

The recommended stepwise approach to treatment in children, especially in children <5 years, begins with the gold standard low dose daily inhaled steroids. The majority of patients will respond to this without the need to escalate to a low double dose or specialist assessment. Unfortunately, current treatment paradigms do not modify the evolution of the disease and withdrawal of treatment will result in manifestation of symptoms and pulmonary function, similar to an untreated individual at the same disease stage.[42]

Several components are needed to achieve asthma control. First, the most appropriate treatment must be chosen for the patient. In the majority of patients with mild asthma, adequate treatments exist to achieve disease control; however, other factors need to be addressed that may impinge on the ability of the patient to control their asthma. Economic difficulties may impede access to treatment, lack of parental education may affect aspects of control, spacers may be needed and should be provided where necessary, lack of adherence (˜70%) must be addressed, and risk factors or triggers such as smoking should be reduced as much as possible. The above measure will also be useful in the 5% of patients with severe asthma who are at greatest risk of exacerbations.

Managing Wheezing and Asthma Exacerbations

Control of asthma means different things to different people. From the patient's perspective, control may mean the ability to live a full life, attend work or school, take part in activities, and achieve undisturbed sleep. The physician will often focus on long-term outcomes, avoiding overuse of steroids, for example, due to long-term effects on bone density. From the perspective of the healthcare system as a whole, reducing cost and disease burden are the Holy Grail. Happily, maintaining physiological control and avoiding exacerbations can achieve all these goals in the long term.

Current Control

A logarithmic relationship exists between lower Asthma Control Test scores, indicating worse control, and higher odds of exacerbations.[43] Patients with partially controlled and uncontrolled asthma are, respectively, two (OR: 1.97; 95% CI: 1.53–2.54) and six-times (OR: 5.74; 95% CI: 4.52–7.29) more likely to suffer exacerbations compared with patients with full control.[44]

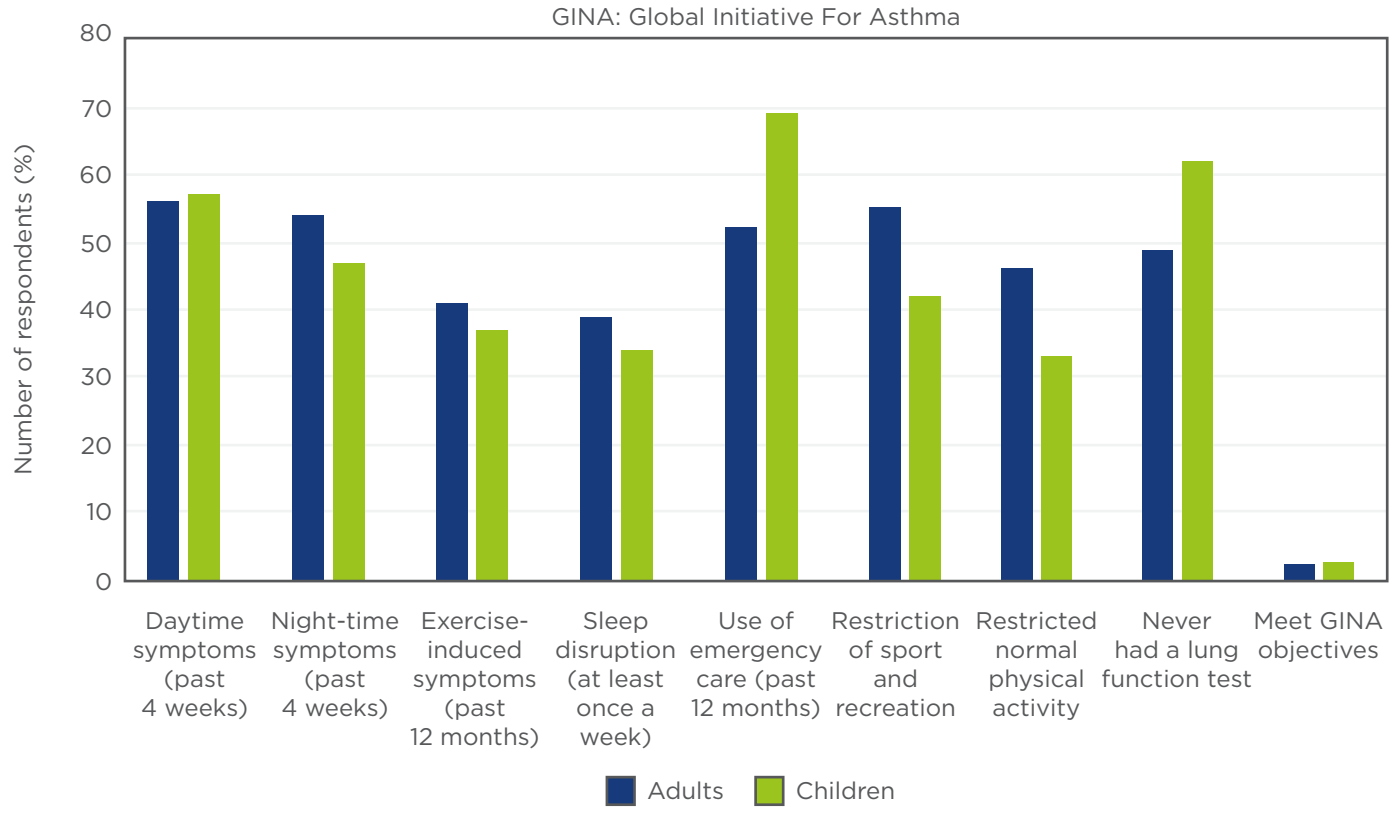

Figure 2: Indices of asthma control in Latin America from the AIRLA study.[45]

Data from 2005 suggest asthma control in Latin America was inadequate during this period. The large Asthma Insights and Reality in Latin America (AIRLA) study[45] (N=2184) surveyed adults with asthma and parents of affected children about healthcare utilisation, symptom severity, activity limitations, and medication use. Almost 50% of adults and children had symptoms every day and night. Symptoms during exercise were common (40%) and the majority of adults reported their ability to exercise was limited. Disruption to sleep and limitation of daily activities were also common. The majority of both adults and children had required an ER visit, with close to three-quarters of children requiring emergency treatment. ER visits were more common in children, likely due to the higher rate of viral infection in this age group. Strikingly, <3% of the patients met GINA criteria from asthma control. An additional cause for concern was the underutilisation of inhaled corticosteroids across all severity groups (mean: 6%), reflecting a general non-adherence to guidelines. Patient perceptions regarding asthma control were far from in line with reality in the AIRLA study. Forty five percent of those surveyed perceived their asthma as well controlled compared with the 2% controlled according to GINA criteria.[45] All data is displayed in Figure 2.

In asthma, as in all chronic disease, the risk of disease development accrues over time with cumulative exposure to risk factors. However, data from the long-term Melbourne asthma study (MESCA), 1964–2007, indicate that despite this long-term accumulation, the greatest single predictive factor for severe asthma at the age of 50 years is severe asthma during childhood.[7] Therefore, the large number of children from the AIRLA study with an occult lack of control due to family misperceptions represent a high risk for future severe illness in the population (Figure 2). Furthermore, recent data indicate there is a significant phenotypic overlap between asthma and chronic obstructive pulmonary disease, and both children and adults with impaired lung function are at increased risk of developing fixed airway obstruction, and possibly chronic obstructive pulmonary disease in early adulthood.[46]

In Finland, a national programme reduced asthma morbidity and its impact on both society and individuals, illustrating the ability to affect long-term positive change.[47] Similar improvements have been achieved in Latin America, where implementation of guidelines based on GINA saw a steady fall in hospitalisations from 1997 onwards. The introduction of affordable corticosteroid care with beclomethasone and its adoption by general practitioners had a further positive impact. Between 1997 and 2011, hospitalisation of children and adolescents reduced by 50–60%, and reductions in adults were 50–74%. There were also marked reductions in mortality in all age groups over this period, evidently related to increased physician awareness and improved prescribing patterns.[48]

Exacerbations and Their Triggers

Whether asthma is well controlled or not, exacerbations tend to be associated with triggering factors. Among various possible factors, viral infection is the most important, particularly in younger children. Approximately 85% of children who experience an acute asthma attack have a viral infection at the time. Among children hospitalised for wheezing, RSV, influenza virus, and rhinovirus are most common in those <3 years old, and rhinovirus is most common in children >3 years.[49] Other risk factors in children <5 years old include uncontrolled asthma symptoms, ≥1 severe exacerbation in the preceding 12 months, season, tobacco smoke, indoor or outdoor air pollution, indoor allergens, psychological or socioeconomic problems, poor adherence or incorrect spacer or inhaler technique, exercise, cold air, and medications.

In children <2 years of age, viral wheezing is often associated with risk factors including tobacco smoke exposure, reduced lung function, and a lack of breastfeeding. In older children, viral wheezing is often associated with elevated IgE, inhaled allergen sensitisation, and maternal asthma. In a Costa Rican study,[50] children with uncontrolled asthma admitted to the ER with an exacerbation were studied and rhinovirus was identified as the major causal agent. Allergic sensitisation to dust mites, demonstrated by high IgE titres, was a significant risk factor for rhinovirus-associated wheeze in these patients (OR: 31.5; 95% CI: 8.3–108.0). These data are in line with a contemporaneous study showing that children sensitised to aeroallergens had a greater risk of developing viral wheeze (hazard ratio: 1.9; 95% CI: 1.2–3.1).[51]

Parasitic infection with *Ascaris lumbricoides* is a region specific environmental risk factor for asthma exacerbations in Costa Rica. Patients infected with *A. lumbricoides* displayed eosinophilia, decreased lung function, and increased airway

hyper-responsiveness, alongside increased risk of hospitalisation for asthma (OR: 3.08, 95% CI: 1.2–7.7).[52] Air pollution is another particularly pressing issue within the Latin American region and one likely to deteriorate due to climate change.[53-55] Indoor pollution is associated with increased asthma symptoms and use of rescue medication. The issue is particularly prevalent in association with poverty and the use of combustible fuel to cook indoors.[56] Unsurprisingly, data from meta-analyses indicate that parental and passive smoking increase the risk of wheezing (OR: 1.41) and asthma (OR: 1.85) in children <2 years old and the risk of developing asthma in children of ages 5–18 years (OR: 1.23).[57]

The impact of diet and vitamin D deficiency has also been investigated in Costa Rican children with asthma (N=616). The 28% of children with levels of vitamin D below guideline recommendations had the highest levels of IgE and eosinophils, more visits to the ER and hospitalisations, more anti-inflammatory treatment, and more bronchial hyperactivity.[58]

As previously noted, poverty is associated with risk factors for asthma exacerbations. The cycle of poverty drives people towards disease and impedes their ability to control it. Poverty limits socioeconomic opportunities resulting in risky behaviour and increased exposure to risk factors for asthma. When disease has taken hold, limited access to healthcare compounds the likelihood of exacerbations which may, in turn, lead to work absences and increased poverty, further compounding the situation.

Exacerbation Management

Asthma exacerbations are a medical emergency leading to a dramatic short-term decrease in lung function followed by a return below the previous baseline level. The result is a progressive deterioration in lung function, which is more marked in severe cases. Their main clinical feature is reduced expired airflow which may be measured by wheezing, progressive dyspnoea, hyperventilation leading to hypoventilation, and by testing pulmonary function (forced expiratory volume in the first second).[59,60] Factors increasing the likelihood of death from an asthma exacerbation include a previous near-fatal exacerbation, previous intubation, hospitalisation in the previous year, >2 previous ER visits, use of oral corticosteroids or short-acting β2 agonists for control, and psychosocial issues.[61]

Pathophysiologically, three conditions occur during an exacerbation: bronchoconstriction, inflammation, and hypoxaemia. These are corrected with early use of short-acting β2 agonists, steroids, and oxygen, respectively. Nebulisers are no longer recommended for the management of asthma due to increased application and waiting time, higher cost, and lack of portability. Inhalers or spacers, with education for proper use, have the advantage of a lower application time with no wait, lower cost, and portability. Children in crisis treated with a salbutamol inhaler at home are likely to arrive at hospital in a significantly better state than those not treated at home. However, spacers must be the appropriate size for the patient, allow rapid inhalation of the corticosteroid, and be applied in a manner that does not further restrict breathing.

The majority of treatment guidelines in Latin America and worldwide follow a similar path to those recommended by GINA. The first stage is examination to determine if the exacerbation is mild, moderate, or severe/life-threatening. In a mild or moderate crisis, the patient should be started on short-acting β2 agonists immediately, plus oxygen if needed. Steroids are not recommended unless the crisis is severe requiring hospitalisation, due to deleterious effects on bone development. Magnesium sulphate may be used as a second-line medication for patients >12 years of age who are experiencing a severe crisis. Following improvement, a short-acting β2 agonist should be continued during the observation period and the opportunity taken to educate the patient or parent regarding use of inhalers or spacers, risk factors, and other factors which may improve control.

Two aspects of treatment are often overlooked: time for recovery and prevention. Prevention can be aimed at better use of medication including proper use of inhalers, adherence to treatment, side effects, use of spacers, costs, and availability. Non-medication-related prevention covers education regarding risk factors, especially respiratory infections through washing hands and avoiding contact with sick people, reducing indoor and outdoor pollution, and improving nutrition and exercise.

The medical community has effective medications, effective evidence-based guidelines, and an active research community collaborating at an international level. However, it lacks resources, time to educate patients, proper compliance from patients, control of disease, and risk factors, local cohort studies and, most fundamentally, a cure.

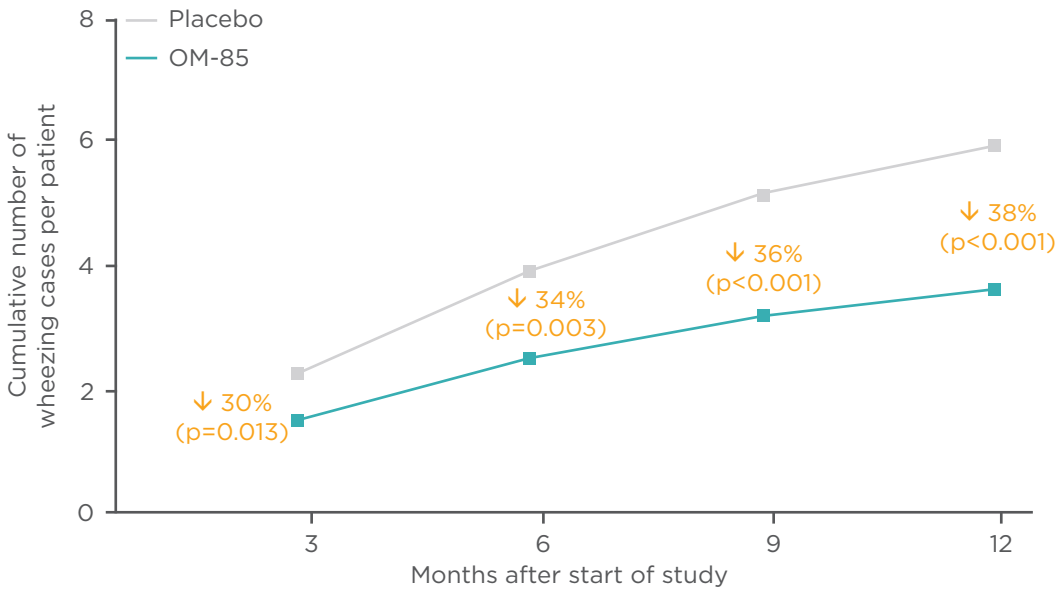

Figure 3: Effect of OM-85 prophylaxis in pre-school children with a history of recurrent viral wheeze.
Adapted from Razi et al.[63]

Progress towards these unmet needs is required to meet the medical community's responsibilities to patients.

Immunomodulators: Role in the Prevention of Asthma Development and Exacerbations?

Multiple precipitating factors may initiate an asthma exacerbation, from temperature change to allergens, pollutants, stress, exercise, infection, or smoking. Preventative measures, such as the use of immunomodulators, may reduce the immune system's responsiveness to these triggers and thus reduce the extent of the exacerbation.

Currently, there are promising results from five studies of the bacterial lysate immunomodulator OM-85 for the prevention of wheezing or asthma in children. In a small randomised single-centre study conducted in China, infants hospitalised with wheezing, who required oxygen support, glucocorticoid, or bronchodilator treatment were randomised to receive post-discharge OM-85 (n=24) (standard dosing: 3.5 mg/day for 10 days/month for 3 months) or standard dosing or budesonide aerosol 200 µg once or twice daily (n=19). A group of untreated healthy controls was also included in the study (n=10). During the 1-year follow-up, there was a 38% reduction in the risk of recurrent wheezing. Only 25% of the infants suffered recurrent wheeze after receiving OM-85 compared with 63% receiving inhaled steroids (p<0.05).[62]

A double-blind, randomised, placebo-controlled, parallel-group study on OM-85 in patients aged 1–6 years, with virus-induced recurrent wheezing was carried out in Turkey. Seventy-five children received OM-85 or placebo (standard dosing) with a 1-year follow-up. OM-85 reduced the number of wheezing attacks by 38% over 12 months (Figure 3) (mean difference: 2.18; 95% CI: 3.22–1.13; p<0.001) and the difference was highly significant from 9 months onwards (p=0.001). In line with the relationship between infection and wheezing events, the number of acute respiratory tract infections (RTI) (-2.44 [-3.5 to -1.36]; p<0.001) and episodes of nasopharyngitis (-2.11 [-2.94 to -1.27]; p<0.001) was reduced over the 12 months, with a highly significant reduction from 6 months onwards for both conditions (p<0.001). Patients treated with OM-85 also achieved a reduction in the cumulative number of wheezing days per patient and duration of wheezing attack (p<0.001). The authors concluded that OM-85 was a useful complementary treatment to reduce the number and duration of RTI-induced wheezing attacks in pre-school children.[63] It is worth keeping in mind the phenotypic differences in wheeze in patients between the ages of 1 and 6 years, which may have affected the results.

A 1-year, single-centre, prospective, open-label study compared OM-85 (n=29) to inhaled corticosteroids (n=16) in school children with acute stage asthma. The choice of study arm was left to the participants, introducing a selection bias.

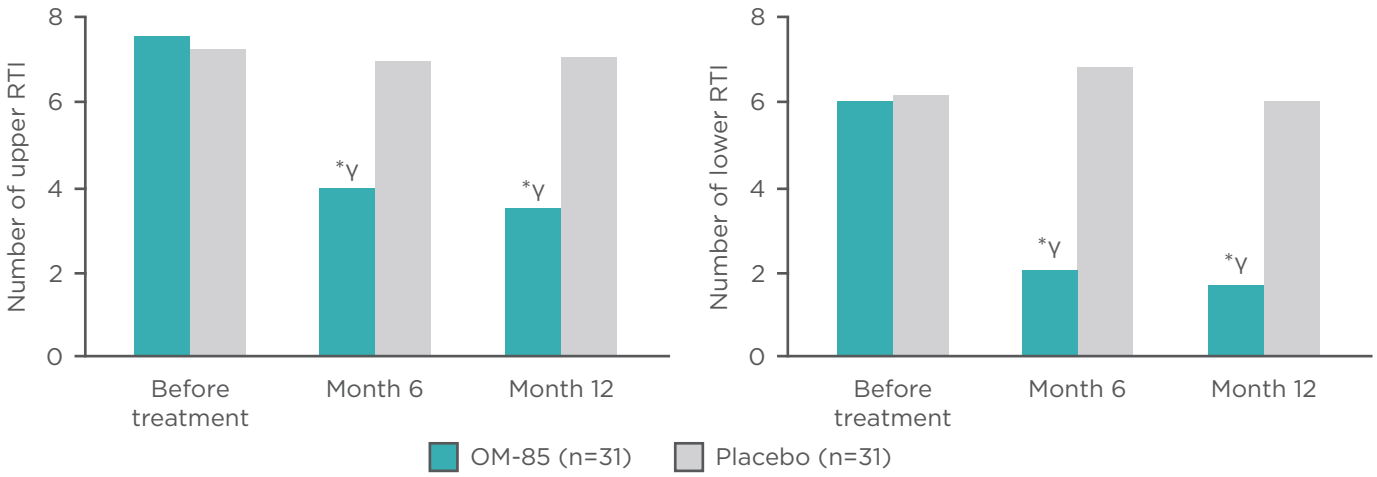

Figure 4: Number of upper respiratory tract infections and lower respiratory tract infections in patients receiving OM-85 prophylaxis or placebo.

*p<0.01 (versus placebo); ᵞp<0.05 (versus before treatment).

RTI: respiratory tract infection.

Adapted from Liao and Zhang[65]

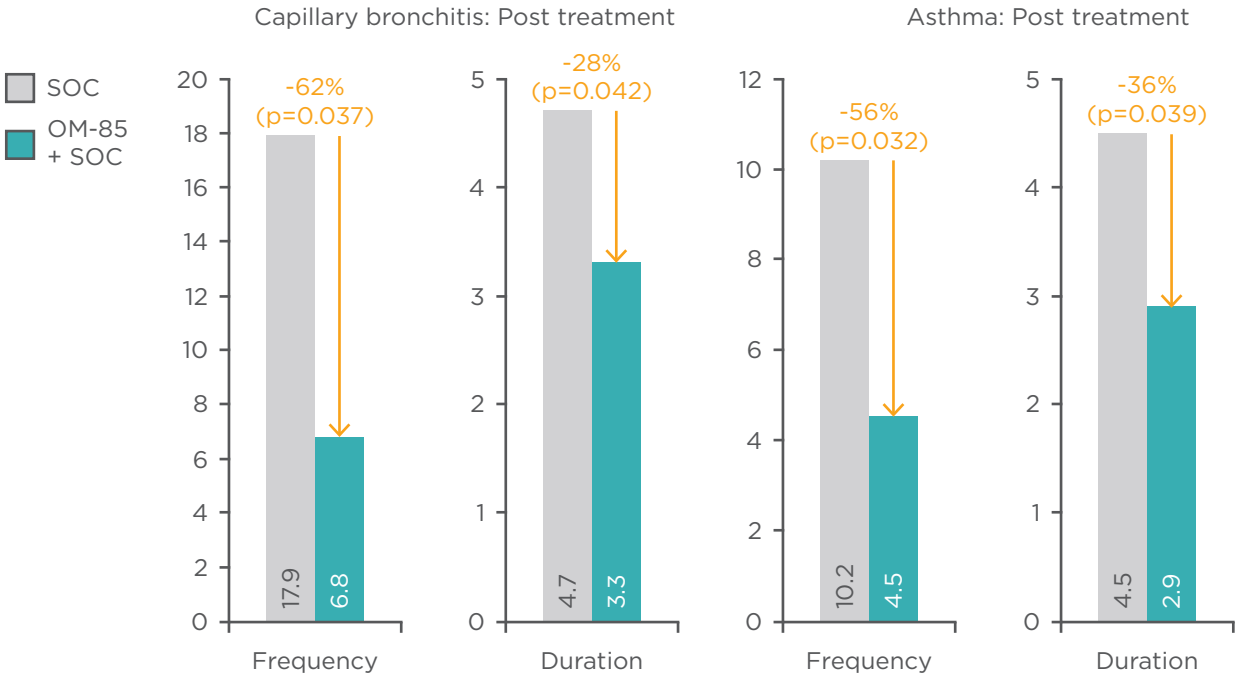

Figure 5: Frequency of capillary bronchitis and asthma exacerbations following addition of OM-85 to standard of care versus standard of care alone.

SOC: Standard of care.

Adapted from Han et al.[66]

OM-85 reduced asthma exacerbations (55% reduction) and respiratory infections (61% reduction). There was a significant corrective effect on the Th1/Th2 cytokine (INF-γ:IL-4) imbalance in both patient groups. Lung function was also improved in the OM-85 group compared with ICS treated patients; however, these results should be interpreted with caution as they were not adjusted for height, sex, or age.[64]

A prospective, randomised, double-blind study compared OM-85 (n=35) prophylaxis or placebo (n=40) in children aged 1–12 years old with asthma and recurrent RTI. The active arm received standard dosing of OM-85 in Months 1–3, and again

in Months 7–9. There were marked reductions in the number of upper and lower RTI (URTI and LRTI) at 6 and 12 months versus baseline ($p<0.05$) and versus placebo ($p<0.01$) (Figure 4). Furthermore, there were significant increases in serum human β-defensin-1, IgA, and IgG in the treatment group compared with baseline at Month 6 and 12 ($p<0.05$) and compared with the placebo group at Month 6 and 12 ($p<0.05$).[65]

A recent randomised trial compared OM-85 in combination with standard of care (n=74) to standard of care alone (n=62) in infants with viral capillary bronchitis and secondary bronchial asthma. Addition of OM-85 to standard of care resulted in significant improvements in capillary bronchitis and asthma at 1-year post-treatment (Figure 5). In addition, there were improvements in IL-17, IL-4, IL-10, and INF-γ levels in the OM-85 group.[66]

Patients at Risk

At-risk patient groups for wheezing who may be considered for OM-85 prophylaxis include pre-term infants, children <6 months of age, children who were never breast-fed, patients with an underlying heart or lung condition (e.g., cystic fibrosis and Down's syndrome), children with a depressed immune system, children exposed to tobacco smoke, and children exposed to crowded environments (e.g., day-care and siblings). As physiological vulnerability decreases with age, exposure increases, keeping the risk for severe bronchitis or wheezing high.

Hospitalisation due to RSV infection is substantially more common in premature babies (6–7%) compared with healthy controls (2–3%). In infants with chronic lung disease, hospitalisation rates approaching 39% may be observed during the first year of life.[67] Children with Down's syndrome are at very high risk of hospitalisation due to alterations in their lung structure. The prevalence of hospitalisation for this group is approximately 10% during the first 2 years of life.[68]

At-risk groups for persistent asthma include those with a parental history of asthma (especially maternal) and allergy; those with eczema or allergic rhinitis; those experiencing persistent wheezing, wheeze without viral infection, or exercise-induced wheeze; those experiencing severe wheezing episodes; patients with allergic sensitisation, especially early poly-sensitisation; and those with increased numbers of eosinophils and fractional exhaled nitric oxide.

OM-85: Future Perspectives and Research

Despite almost 35 years of clinical use, there are still many pending questions regarding the mechanism of OM-85. Currently there are no data examining which of the 21 strains of bacteria contained in OM-85 are essential for its immunomodulatory effect, or if the presence of all the strains is required. The bacterial components and the specific pattern-recognition receptors, likely toll-like receptors, responding to them have yet to be identified. Studies comparing different doses or dosing schedules have not been carried out, and sufficient data on whether activity is equal in patients with allergic and non-allergic wheezing are currently unavailable.

There are currently four ongoing studies investigating OM-85 in wheezing and asthma that may address some of the above questions. The OMPAC study[69] is currently underway in Australia, including 60 infants aged 3–9 months at risk due to a sibling with asthma or atopy. This randomised trial will compare outcomes in infants treated with OM-85 in two cycles during the infants first two winter seasons (3.5 mg; 10 doses/5 consecutive months) versus placebo. The study will compare primary prevention of symptomatic LRTI, persistent asthma development, nasal microbiota, circulating T-regulator cells, allergen sensitisation, and transcriptomics analysis. Results for OMPAC are expected in June 2019.

The ORBEX study[70] is a large, multicentre, randomised, placebo-controlled trial, with upwards of 8 centres in the USA (N=1,076). The objective is to determine if OM-85 (3.5 mg/day for 10 days/month for 2 years) given to infants (6-18 months old) at high risk due to having atopic eczema and/or having a parent or sibling with asthma can increase the time to occurrence of the first episode of wheezing, due to a lower respiratory tract illness during a third observational year after therapy.

Exclusion criteria include more than one previous serious episode of wheezing or more than two mild episodes. Severe wheezing is defined as cough and wheezing >24 hours and one of the following: >6 doses of albuterol in <48 hours, ER visit or hospitalisation, use of inhaled or systemic corticosteroids, diagnosed asthma, or a systemic illness (other than allergy). The primary outcome is time to first wheezing episode during follow-

up. Secondary outcomes include wheezing rate during treatment and during follow-up, time to first wheezing episode during treatment, and the rate of severe wheezing during treatment. Adverse events will be assessed, and DNA, serum, and stool samples will be collected for future genetic studies assessing the bacterial and viral flora. Recruitment will run from January 2017 to December 2018, with preliminary results expected by December 2021.[70]

The Italian OMPeR trial will investigate OM-85 for the prevention of URTIs in children aged 1–5 years at high risk due to mild immunodeficiency (IgA, IgG), atopy, or recurrent wheezing. Children will be randomised to receive OM-85 at standard dosing or placebo, stratified by risk factor. An additional exploratory arm will investigate longer term dosing of 10 days for 6 consecutive months. Prevention of URTI during a 6-month follow-up will be investigated alongside URTI duration and severity, mean number of LRTI, RTI requiring antibiotics, bacterial tonsillitis, acute otitis media, school days lost, antibiotic therapy and cycles, and faecal microbiota. For patients recruited during an active infection at the first visit, time to cure will also be measured. Results are expected in 2018 (Prof S. Esposito, personal communication, 2017).

Finally, the BREATHE study[71] has an alternative goal of improving asthma control. Adolescents and young adults (12–40 years old; N=120) with uncontrolled asthma (GINA 4 and ≥2 asthma exacerbations during previous winter season, Asthma Control Questionnaire >1.5) will be randomised to receive either OM-85 at 7 mg/day for 10 consecutive days during the October–March viral season for two consecutive seasons, or placebo. Following the 18-month treatment period, spanning two winters, there will be a 1-year follow-up. Reduction of asthma exacerbations, including suspected infectious exacerbations, will be assessed alongside nasopharyngeal/faecal microbiome and inflammatory markers in serum or sputa. Results are expected in 2020.[71]

The Next Steps

Two previously mentioned at-risk groups, pre-term infants and infants with Down's syndrome, offer opportunities for research into putative unmet clinical need for OM-85 prophylaxis. The scale of this unmet need in Latin America is illustrated by a Brazilian longitudinal birth cohort study in pre-term infants (N=310), BREVI, which showed extremely high rates of LRTI (58%) and severe LRTI (21%), 61% of which were associated with RSV.[72] Given the large number of infants hospitalised for RSV alone (n=56), the investigation of the putative ability of OM-85 to reduce hospitalisations in this population should be a priority.

CONCLUSION

The prevalence of asthma is increasing worldwide, and is associated with substantial economic and humanitarian effects. Viral infections are important in the development and exacerbation of asthma, alongside a complex interaction between genes and the environment. RTI cannot be avoided completely and contact with micro-organisms is a necessity of immune system maturation. However, immunomodulators offer a dual protective mechanism via creating pre-alert immune state which reduces infection rate and by reducing excess inflammatory processes. The immunomodulator OM-85 reduces URTI, LRTI, and wheezing in children and studies are underway investigating the effect of OM-85 on the prevention of asthma in high-risk children.

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