Factors predicting the presence of Legionella pneumophila and Mycoplasma pneumoniae in community-acquired pneumonia

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" FACTORS PREDICTING THE PRESENCE OF *LEGIONELLA PNEUMOPHILA* AND *MYCOPLASMA PNEUMONIAE* IN COMMUNITY-ACQUIRED PNEUMONIA"

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Contexte

Un défi lors de pneumonie acquise en communauté (PAC) non sévère est d'évaluer si une bactérie atypique, en particulier *Legionella pneumophila* et *Mycoplasma pneumoniae,* pourrait en être la cause. Le dilemme à résoudre est le suivant : est-il préférable d'élargir la couverture antibiotique pour y inclure les pathogènes atypiques, prévenant ainsi un décours potentiellement sévère, ou peut-on utiliser un antibiotique avec un spectre d'action plus étroit, afin de diminuer les risques d'interactions médicamenteuses, les effets indésirables, la pression de sélection antimicrobienne et les coûts de la santé ? De plus, comme le diagnostic microbiologique prend souvent du temps et que l'étiologie reste dans la majorité des cas inconnue, la décision de couvrir un pathogène atypique se fait le plus souvent empiriquement, en se basant uniquement sur l'anamnèse, ainsi que l'examen physique et quelques examens complémentaires de routine. Dans cette perspective, il serait utile d'identifier les paramètres cliniques disponibles à l'admission permettant de prédire la présence de *L. pneumophila* ou *M. pneumoniae* comme pathogène causal de la PAC.

Méthodologie

Ce travail confronte les paramètres cliniques associés à la présence de pathogènes atypiques identifiés lors d'une revue systématique de la littérature avec ceux mis en évidence dans une population de 580 patient·e·s hospitalisé·e·s pour une PAC entre 2009 et 2013 et inclus·es dans un essai clinique Suisse multicentrique. Une analyse statistique univariée et multivariée a permis d'identifier les facteurs associés de manière indépendante à la présence d'un pathogène atypique, permettant de dériver un score prédictif. La précision du score pour prédire la présence d'un pathogène atypique a ensuite été évaluée.

Résultats

Dans l'analyse statistique univariée, l'insuffisance cardiaque, l'état confusionnel, un taux sérique élevé de protéine C-réactive (CRP) et une hyponatrémie étaient des facteurs prédisant la présence de pathogènes atypiques, tandis que la présence de douleur thoracique était un facteur prédictif négatif. Une insuffisance cardiaque, une consommation abusive d'alcool, un état confusionnel, une CRP élevée et une hyponatrémie étaient des facteurs prédictifs positifs pour *L. pneumophila*, alors que la présence d'une toux et d'une hypoxémie étaient négativement associées. Les pathogènes atypiques ainsi que *L. pneumophila* étaient plus fréquents en automne. Un compte leucocytaire plus faible est l'unique facteur prédictif pour *M. pneumoniae*.

Dans l'analyse multivariée, un âge inférieur à 75 ans, une insuffisance cardiaque, l'absence de douleur thoracique, une hyponatrémie et la survenue de la maladie en automne étaient tous des facteurs prédictifs positifs indépendants pour la présence de pathogènes atypiques. Ainsi, un score prédictif abrégé par l'acronyme « CASH-75 » a été dérivé avec une aire sous la courbe (AUC) à 0,78 (IC 95% = 0,71-0,85, valeur $p < 0,001$). Un seuil a été identifié dans le but de prédire l'absence de pathogènes atypiques avec une sensibilité et valeur prédictive négatives élevées.

Conclusion

Cette étude a identifié des facteurs faciles à obtenir à l'admission et prédisant de manière indépendante la présence de *L. pneumophila* et *M. pneumoniae* chez des patient·e·s adultes hospitalisé·e·s pour une PAC non-sévère. En utilisant le score CASH-75, la présence d'une bactérie atypique pourrait être exclue raisonnablement chez un certain nombre de patient·e·s. Sous réserve d'une validation dans d'autres cohortes, l'utilisation de ce score permettrait de restreindre le spectre antibiotique utilisé dans le traitement de la PAC, ce qui diminuerait les résistances bactériennes, les effets médicamenteux indésirables, et les coûts de la santé.

Introduction (français)

Contexte

La pneumonie est une infection du parenchyme pulmonaire qui est à la fois fréquente et potentiellement mortelle. Les symptômes, tels que la toux, la dyspnée ou la fièvre ne sont pas spécifiques et peuvent être provoqués par d'autres pathologies fréquentes. Ainsi, le diagnostic est confirmé principalement grâce à une radiographie conventionnelle thoracique ou un autre type d'imagerie, qui permettent de distinguer la pneumonie d'autres maladies respiratoires, infectieuses ou inflammatoires[1]. La pneumonie peut être classée en différentes catégories selon le contexte d'acquisition de la maladie. La pneumonie acquise en communauté (PAC) est définie comme une pneumonie apparue à moins de 48 heures d'une admission hospitalière, par contraste avec la pneumonie nosocomiale. La catégorie de pneumonie liée aux soins[2,3], regroupant des patients non-hospitalisé·e·s mais en contact fréquent avec le système de santé, avait pour but de servir de facteur de risque pour la présence de bactéries multi-résistantes[2], mais s'est avérée trop peu précise pour être utile. Ainsi, la Société Thoracique Américaine (American Thoracic Society) et la Société des Maladies Infectieuses Américaine (Infectious Disease Society of America) ont recommandé d'abandonner cette nomenclature en 2019, celle-ci ayant engendré un usage croissant d'antibiotiques à large spectre sans pour autant améliorer le pronostic des patient·e·s[4]. Ainsi, la pneumonie est aujourd'hui catégorisée en PAC, pneumonie nosocomiale, avec une sous-catégorie de pneumonie liée à la ventilation mécanique, et enfin la pneumonie de l'hôte immunocompromis.

Alors que la pneumonie était traditionnellement considérée comme principalement bactérienne, de récentes études montrent que les virus sont responsables d'au minimum un cas sur cinq[5,6]. Par ailleurs, dans la majorité des cas, un pathogène ne peut être incriminé[5,7]. La cause bactérienne la plus fréquente est *Streptococcus pneumoniae*, qui est considéré comme un germe typique, avec *Haemophilus influenzae* et *Moraxella catarrhalis*[8]. Toutefois, des pathogènes dits atypiques peuvent aussi causer des pneumonies, tels que *Mycoplasma pneumoniae, Legionella pneumophila*, *Chlamydia pneumoniae* et moins fréquemment trois zoonoses : *Chlamydia psittaci, Francisella tularensis* et *Coxiella burnetii*[8,9].

Les infections des voies respiratoires inférieures, telles que la pneumonie, sont la quatrième cause de décès et la deuxième cause d'année de vie perdues sur le plan mondial[10]. En Europe et aux États-Unis d'Amérique, la PAC est la première cause de mort due à une infection[11]. En Europe, la PAC a une incidence de 1,07 à 1,2 pour 1000 personnes-années, qui augmente jusqu'à 14 pour 1000 personnes-années chez les plus de 65 ans[12]. En Suisse, un total de 22'928 hospitalisations pour cause de pneumonie ont été enregistrées en 2019[13]. Puisque la PAC touche principalement les personnes plus âgées et que la population tend à vieillir, une augmentation des hospitalisations pour cette cause est attendue dans les années à venir[11,12].

Les facteurs de risque principaux pour une PAC peuvent être classés en trois catégories : constitutionnels, tels qu'un âge avancé et le sexe masculin ; occupationnels ou liés à des habitudes, tels que le tabagisme, l'abus d'alcool et un contact avec des enfants ; et enfin ceux liés aux comorbidités, tels qu'un mauvais état nutritionnel, une mauvaise santé dentaire, une maladie respiratoire ou cardiovasculaire chronique, une maladie de Parkinson, une épilepsie, une démence, une dysphagie ou encore une maladie hépatique ou rénale chronique[12].

Les pathogènes atypiques

Historiquement, la distinction entre pneumonie typique et atypique était basée sur la clinique, la pneumonie atypique présentant des manifestations extrapulmonaires, comme une méningoencéphalite, péricardite, myocardite ou des symptômes gastro-intestinaux (ex : diarrhées aqueuses), que l'on pouvait interpréter comme un syndrome[8,14]. Néanmoins, il est maintenant clair qu'en pratique cette discrimination n'est pas possible, que ce soit d'un point de vue clinique ou radiologique[15,16]. Actuellement, la distinction entre bactéries typiques et atypiques est centrée autour d'une différence majeure d'un point de vue microbiologique : le caractère intracellulaire des pathogènes atypiques. Ceci a pour conséquence de rendre ces bactéries résistantes aux antibiotiques conventionnels utilisés pour traiter *S. pneumoniae*[17], tout en répondant aux macrolides, tétracyclines et fluoroquinolones[14]. Toutefois, du fait des nombreux points communs de la clinique des deux groupes de pathogènes, certains experts considèrent cette distinction comme obsolète et préfèreraient l'abandonner[14]. Cependant, cette catégorisation reste très utile pour discuter du traitement empirique lors de pneumonie. Malgré que les antibiotiques efficaces contre les agents atypiques restent souvent également efficaces contre les bactéries typiques, ils n'en sont pas le traitement de choix, soit du fait d'un spectre trop large favorisant l'apparence de bactéries multirésistantes (fluoroquinolones), soit du fait de la présence de résistances chez les pathogènes typiques (macrolides et tétracyclines)[14].

La prévalence globale de PAC causée par une bactérie atypique dans la population adulte est de 14%[18], avec une grande variabilité entre les études. Tandis que les pathogènes atypiques sont classiquement considérés comme infectant principalement les enfants et jeunes adultes, Lui et coll.[19] ont montré qu'ils sont cependant présents dans 11,2% de toutes les pneumonies chez l'adulte et dans 28,6% lorsque un pathogène a pu être incriminé. Ils peuvent aussi infecter les plus âgé·e·s, comme l'ont démontré Maruyama et coll. [20] en observant que les pathogènes atypiques représentent 44,7% des PAC chez les 85 ans et plus. Toutefois, d'autres études ont retrouvé des prévalences plus faibles : une prévalence de pathogènes atypiques de 2% chez les plus de 80 ans dans une étude[21] ;et une prévalence de *L. pneumophila* chez les personnes âgées variant entre 0 et 15% dans une méta-analyse[22].

Chlamydia pneumoniae a été identifiée comme une cause fréquente de pneumonie dans d'anciennes études basées sur des sérologies, avec une prévalence estimée à environ 10%[23]. Toutefois, des études plus récentes, où le diagnostic était posé grâce à une réaction en chaîne par polymérase (PCR), montrent une prévalence beaucoup plus faible qu'initialement décrite, soit moins de 1%[24,25]. Cela contredit donc la haute prévalence décrite précédemment avec les études sérologiques, la séroprévalence croissante avec l'âge[26] n'étant pas synonyme que cette bactérie soit l'agent causal de la pneumonie.

De manière générale, toutes les pneumonies zoonotiques, soit *C. burnetii, F. tularensis* et *C. psittaci,* sont très rares dans nos régions et peuvent être raisonnablement exclues du diagnostic différentiel grâce à une anamnèse prenant en compte les expositions animales[8,27,28]. Pour ces raisons, nous ne nous attarderons pas sur ces pathogènes. Ainsi, l'étude actuelle se concentrera sur les deux pathogènes atypiques majeurs : *L. pneumophila* et *M. pneumoniae*.

Legionella pneumophila

L. pneumophila a été pour la première fois décrite suite à l'épidémie survenue en 1976 à la convention de la Légion Américaine à Philadelphie[29]. Il s'agit d'un bacille Gram négatif, intracellulaire facultatif, aérobe obligatoire et non fermentateur[29–31]. Cette bactérie contamine les sources d'eau douce en vivant dans des amibes, qui forment un biofilm dans les eaux stagnantes ayant une température entre 20 et 70°C. Dans le corps humain, elle colonise les macrophages des voies respiratoires[27,31–33]. La voie d'infection se fait donc uniquement via un contact direct avec l'environnement contaminé ou à travers des aérosols de cette même source (ex : tour de refroidissement, spa …), mais jamais de façon interpersonnelle[32,34–37]. Si la source n'est pas contrôlée, une épidémie peut se déclarer[38–40], raison pour laquelle *L. pneumophila* est à déclaration obligatoire en Suisse[41]. Cette bactérie est plus fréquente en été et au début de l'automne lorsque le temps est humide et chaud[42–45]. De plus, cette période coïncide avec les voyages vacanciers et en effet, 1 légionellose sur 5 est associé au voyage. Ce phénomène a deux éléments causatifs : contracter la maladie lors du voyage où des sources d'eau sont contaminées et contracter la maladie au retour de voyage, suite à la stagnation de l'eau du domicile[31]. La période d'incubation est de 2 à 10 jours[31].

L. pneumophila infecte plus souvent les personnes âgées, épargnant les jeunes adultes et est extrêmement rare chez les enfants[18,36,45,46]. Mondialement, ce pathogène est responsable de 3% des pneumonies[18] et en Suisse 376 cas par an ont été déclarés en moyenne entre 2010 et 2019, avec une augmentation constante de l'incidence sur les deux dernières décennies[47]. L'augmentation de l'incidence pourrait être expliquée par une meilleure identification des cas, le vieillissement de la population et le changement climatique provoquant des températures plus élevées et des pluies plus fortes[31].

L. pneumophila est le troisième pathogène le plus fréquent dans la PAC sévère[48], ce qui en fait un facteur de risque indépendant pour une PAC sévère[48], avec un taux de mortalité entre 10 et 20%[46,49–52]. Comme manifestations extrapulmonaires, cette bactérie peut causer spécifiquement une hépatite et une atteinte rénale[8,14]. De plus la légionellose est souvent décrite comme un syndrome[53], chaque signe à part n'étant pas pathognomonique, mais la constellation de tous les signes devenant plus spécifique[27]. Chez certain·e·s patient·e·s, *L. pneumophila* peut aussi causer la fièvre de Pontiac, un syndrome grippal non sévère et sans pneumonie, qui ne nécessite pas d'antibiothérapie[31].

D'un point de vue diagnostic, la présence de *L. pneumophila* est démontrée principalement grâce à la détection d'antigènes urinaires. Ce test diagnostic a une spécificité d'environ 99%[31] et une sensibilité allant de 56 à 99%[45]. Puisque cet examen ne détecte que le sérogroupe 1 (soit environ 70 à 80% de tous les sérogroupes), un test négatif ne peut exclure avec certitude la présence de ce pathogène[8,14,31,54], surtout si la maladie est modérée[16]. De plus, même si le test reste positif pendant des semaines[8], les antigènes urinaires peuvent nécessiter quelques jours avant de devenir positifs[27,55–58]. La détection de *L.pneumophila* dans les échantillons respiratoires peut s'effectuer par culture sur des milieux spéciaux ou par détection d'acides nucléiques (PCR). Ces échantillons sont cependant difficiles à collecter, car *L. pneumophila* provoque principalement une toux non productive[31,58]. Une sérologie n'est pas utile, car la séroconversion n'a lieu que 6 à 8 semaines après l'infection et peut rester positive pendant des années[31]. L'immunofluorescence n'est utilisée, ayant une sensibilité trop basse[31].

Les options thérapeutiques pour *L. pneumophila* sont les fluoroquinolones respiratoires telles que la moxifloxacine et la levofloxacine, les macrolides, comme l'azithromycine et la clarithromycine, et enfin la doxycycline[31]. Cette bactérie est intrinsèquement résistante aux bêta-lactamines au vue de son mode de vie intracellulaire[59] et de son action inactivant les bêta-lactamines[60].

Mycoplasma pneumoniae

M. pneumoniae a été découvert par Eaton et coll. en 1944 et était donc d'abord appelée l'agent d'Eaton[61]. Il s'agit d'une petite bactérie sans paroi cellulaire[30,61,62], avec un génome de petite taille, ne contenant pas de gènes codants pour une paroi bactérienne typique[63], et des capacités métaboliques restreintes, dépendant par conséquent d'un mode de vie parasitaire intracellulaire[61]. Sa forme filamenteuse permet l'adhésion à l'épithélium respiratoire[32] et une fois installée en intracellulaire, la cellule de l'hôte le protège contre le système mucociliaire[61]. Le pathogène est transmis via des gouttelettes aérosolisées de personne à personne[36], surtout dans des milieux confinés (ex : casernes militaires, établissement de soins …) où des taux d'attaque allant de 25 à 71% ont été rapportés[61]. Cette bactérie est endémique tout le long de l'année, mais a une plus grande prévalence relative durant l'été, période où les virus respiratoires sont moins fréquents[61], et cause occasionnellement des épidémies tous les 4 à 6 ans[18,32,64–66]. La période d'incubation dure 1 à 3 semaines[61].

M. pneumoniae atteint habituellement les adolescent·e·s et jeunes adultes[67,68], mais peut aussi causer des pneumonies parmi les plus âgé·e·s[69,70]. Cette bactérie cause 7% des pneumonies au niveau mondial[18] et en Suisse, 463 patient·e·s ont été hospitalisé·e·s pour cette raison en 2019[13].

La plupart du temps, *M. pneumoniae* engendre une PAC modérée et autolimitée, qui peut souvent être traitée ambulatoirement, raison pour laquelle on la dénomme aussi *walking pneumonia* en anglais[14,32,61]. Hormis les symptômes pulmonaires, ce pathogène peut spécifiquement provoquer des atteintes dermatologiques[8,32,64], un syndrome de Guillain-Barré[32,71,72] et des troubles hématologiques (ex : agglutinines froides)[32,64]. *M. pneumoniae* est aussi associée à des affections des voies respiratoires supérieures et est incriminée dans l'exacerbation, voire même l'apparition, d'un asthme[8] au travers du relargage de cytokines pro-inflammatoires[61]. Dans des modèles animaux, un rôle de potentialisation de l'infection à *S. pneumoniae* a aussi été décrit[14].

L'outil diagnostic le plus fréquemment utilisé est la PCR sur des expectorations ou un frottis naso-pharyngé. En outre, une étude récente sur une population pédiatrique suggère que la PCR des voies respiratoires supérieures ne peut en fait pas différentier une réelle infection d'un simple portage de ce pathogène[73]. La culture est possible mais fastidieuse et rarement réalisée[64] ; un diagnostic sérologique peut être posé si les taux d'immunoglobulines M (IgM) sont élevés, mais des immunoglobulines G (IgG) augmentées seraient seulement témoin d'une infection passée[8].

Pour *M. pneumoniae*, les possibilités de traitement sont les fluoroquinolones respiratoires, les tétracyclines, comme la doxycycline et la minocycline, et enfin les macrolides. Cette dernière option est particulièrement utile chez les enfants chez qui les deux autres classes sont relativement contre-indiquées[74]. Là aussi, les bêta-lactamines ne sont pas efficaces, car elles agissent sur la paroi cellulaire dont *M. pneumoniae* est dépourvu [64].

Traitement : lignes directrices actuelles

D'un point de vue thérapeutique, différentes lignes directrices, ou *guidelines* en anglais, existent. Toutes convergent pour proposer un traitement combinant une betalactamine et un antibiotique couvrant les pathogènes atypiques chez les patient·e·s présentant une pneumonie sévère, typiquement admis·es aux soins intensifs. Les recommandations concernant les pneumonies de sévérité moyenne, typiquement les patient·e·s hospitalisé·e·s en milieu non-intensif, sont par contre plus diverses.

Selon la guideline « S3 » commune à l'Allemagne, l'Autriche et la Suisse[75], le traitement des patient·e·s hospitalisé·e·s pour une PAC sévère est composé d'une bêta-lactamine à large spectre et d'un macrolide, afin de couvrir toutes les étiologies possibles, typiques comme atypiques et car les macrolides auraient aussi une action immunomodulatrice[76]. Néanmoins, lorsqu'il s'agit d'une PAC de gravité faible à modérée, c'est au médecin de décider s'il veut ajouter un macrolide à la bêta-lactamine. Pour rappel, sans macrolide, les pathogènes atypiques ne sont pas couverts[19].

Les lignes directrices communes de la Société Respiratoire Européenne et de la Société Européenne des Maladies Infectieuses[77] recommandent aussi l'usage empirique d'une bêta-lactamine plus ou moins un macrolide pour les patient·e·s hospitalisé·e·s sans besoin de soins intensifs. Elles recommandent une combinaison d'antibiotiques principalement chez les patient·e·s à plus haut risque. Les recommandations communes de la Société Thoracique Américaine et de la Société des Maladies Infectieuses Américaine[4] recommandent comme traitement empirique des cas de gravité faible ou modérée une bithérapie, composée d'une bêta-lactamine et d'un macrolide, ou une monothérapie à base de fluoroquinolone respiratoire (levofloxacine ou moxifloxacine).

Pourquoi ne pas couvrir systématiquement les pathogènes atypiques chez tou·te·s les patient·e·s atteint·e·s de PAC ? En bref, les raisons sont les suivantes: interactions médicamenteuses, effets indésirables, pression de sélection induisant une résistance bactérienne et coûts plus élevés[78].

En ajoutant un macrolide, le/la patient·e risque des interactions médicamenteuses à travers l'action inhibitrice du CYP3A4, ce qui peut interagir avec la métabolisation d'autres médicaments par ce complexe enzymatique[79,80]. Cependant, contrairement à la clarithromycine et à l'érythromycine, l'azithromycine n'interagit pas avec le CYP3A4[80]. D'autres interactions médicamenteuses pharmacocinétiques sont aussi possibles via l'accélération de la vidange gastrique et via l'effet antibiotique sur la flore commensale (comme tout autre antibiotique)[80]. Les effets indésirables gastro-intestinaux sont les plus fréquents, notamment avec l'érythromycine[81]. Les macrolides sont aussi liés à des évènements cardiovasculaires tels que le syndrome coronarien aigu et une prolongation de l'intervalle QT, surtout avec l'érythromycine[55,82]. Toutefois, les macrolides gardent un profil relativement sûr et ont été pour cette raison largement prescrits, représentant 10 à 15% du marché mondial d'antibiotiques oraux[81]. Cela favorise malheureusement une augmentation des résistances bactériennes[56,64,78], à l'échelle individuelle ainsi que communautaire. Ce phénomène est particulièrement alarmant pour *M. pneumoniae*[83,84], les souches résistantes représentant jusqu'à 95% dans certaines parties de la Chine[74], avec un impact négatif direct sur l'évolution de la maladie[64]. En Europe, la résistance aux macrolides semble moins fréquente, surtout chez les adultes où elle n'a été décrite que sporadiquement, avec une prévalence de résistance chez *M. pneumoniae* variant entre 1,3% des PAC en Italie[85] et 3,1% en Allemagne[68]. Cependant, la surveillance de ces

résistances en Europe est inconstante, ce qui peut mener à une sous-estimation de l'étendue du problème[86].
Les fluoroquinolones respiratoires causent communément des effets secondaires modérés tels que des troubles gastro-intestinaux et des céphalées, mais aussi plus rarement des effets indésirables plus sévères comme une prolongation de l'intervalle QT, des ruptures tendineuses, une dérégulation de l'équilibre glycémique, des atteintes rénales et des crises épileptiques[87]. La prolongation de l'intervalle QT est de plus une source de préoccupation à cause des interactions médicamenteuses potentielles. Les fluoroquinolones ont aussi un effet toxique sur le cartilage de croissance et sont pour cette raison contre-indiquées chez les enfants et pendant la grossesse et l'allaitement[88,89]. Avec leur vaste spectre d'action, notamment via l'efficacité de la levofloxacine et de la moxifloxacine sur les pathogènes Gram positifs, et leur bonne biodisponibilité orale, les fluoroquinolones ont été largement prescrites pour une gamme d'indications. Cet usage intensif a été directement corrélé à l'émergence de bactéries multirésistantes (MDR), par exemple des entérobactéries productrices de beta-lactamases à large spectre (ESBL) et de *Staphylococcus aureus* résistant à la méthicilline (MRSA)[90,91]. Elles sont mises en cause dans les colites pseudomembraneuses iatrogènes dues à *Clostridoides difficile*[91,92]. Il est cependant important de garder à l'esprit que la plupart des antibiotiques peuvent causer une infection à *C. difficile.*
Les tétracyclines peuvent provoquer communément une anorexie, des troubles gastro-intestinaux, un rash et une photosensibilité[74]. Elles peuvent aussi causer une décoloration dentaire chez les enfants et sont ainsi contre-indiquées chez les enfants âgés de moins de 8 ans[93]. Tandis que les résistances aux fluoroquinolones et aux tétracyclines chez *L. pneumophila* et *M. pneumoniae* ne sont pas actuellement un problème d'un point de vue santé publique, des cas de résistance ont déjà été décrits[94,95] et on ne peut exclure que cela devienne une réelle problématique dans le futur.

Prédire la présence de pathogènes atypiques

Ainsi, il existe un dilemme entre couvrir les pathogènes atypiques afin d'éviter des manifestations extrapulmonaires et un décours potentiellement sévère avec *L. pneumophila*, et ajouter inutilement un autre antibiotique qui pourrait engendrer des effets secondaires et des résistances bactériennes. Ceci incite à trouver un moyen de détecter cliniquement si une PAC est causée par un pathogène atypique. Ainsi le traitement empirique peut être rapidement débuté tout en étant le plus ciblé possible, couvrant les bactéries atypiques seulement lorsque nécessaire.
L'enjeu premier est que cette décision thérapeutique doit être prise rapidement dans le but de commencer l'antibiothérapie correcte dès que la PAC a été diagnostiquée[77]. Malheureusement, un diagnostic microbiologique n'est, dans la pratique, pas posé dans cet intervalle de temps[58] et l'antibiothérapie est débutée empiriquement[17]. De plus, avec plus de la moitié des PAC n'ayant pas d'étiologie microbienne prouvée, le traitement antibiotique reste souvent empirique jusqu'à la fin[5,7]. Ainsi, il existe un grand intérêt à développer un score clinique permettant de prédire la présence de pathogènes atypiques[96] en se basant sur l'information disponible à l'admission à l'hôpital : caractéristiques démographiques du/de la patient·e, comorbidités, symptômes, signes cliniques et examens complémentaires de routine. Si un tel score venait à être à la fois discriminants et faciles à utiliser, moins de temps serait perdu dans l'attente des résultats

microbiologiques, l'antibiothérapie pourrait être d'emblée adéquate et une réduction des coûts de la santé pourrait même être envisagée.
Par conséquent, ce travail pose la question suivante : **Chez les patient·e·s adultes immunocompétent·e·s hospitalisé·e·s pour une pneumonie acquise en communauté non sévère, quelles caractéristiques disponibles à l'admission peuvent prédire la présence de *Legionella pneumophila* ou *Mycoplasma pneumoniae* comme pathogène causal ?** Ce travail émet l'hypothèse qu'il existe des facteurs prédictifs décrits dans la littérature et que ces caractéristiques peuvent aussi prédire la présence de *L. pneumophila* et *M. pneumoniae* dans une population Suisse contemporaine ; et que certains facteurs prédictifs peuvent être raisonnablement utilisés en pratique clinique afin de guider le traitement antibiotique empirique.

Discussion (français)

Dans cette analyse secondaire d'une cohorte de patient·e·s inclus·es de manière prospective, la présence d'une insuffisance cardiaque, l'absence de douleur thoracique, le fait de contracter la maladie en automne, une hyponatrémie et un âge inférieur à 75 ans étaient des facteurs de risque indépendants pour la présence d'un pathogène atypique (*L. pneumophila* ou *M. pneumoniae*) en tant qu'agent étiologique d'une PAC. Un âge plus jeune, une température corporelle plus élevée et un compte leucocytaire abaissé ont été associés dans la littérature avec la présence de pathogènes atypiques[19]. L'hyponatrémie[16,51,77,97–100] a été largement décrite comme facteur de risque pour *L. pneumophila* de même que l'absence de douleur thoracique[52,58,99–102] et contracter la maladie en été ou en automne[31,43–45,103]. L'insuffisance cardiaque a, quant à elle, été décrite à la fois comme un facteur prédictif positif[101,104] et négatif[51,56].
Par la suite, un score utilisant 5 critères cliniques faciles à obtenir par l'anamnèse et les examens de laboratoire de routine, a été créé ; le but du score étant de prédire si la PAC est causée ou non par un pathogène atypique, et de déterminer l'antibiothérapie empirique à utiliser. Ce score est abrégé CASH-75, un acronyme en anglais pour les 5 critères : absence de douleur thoracique (absence of **C**hest pain), contracter la maladie en **A**utomne, natrémie inférieure à 135 mmol/L (**S**odium), présence d'insuffisance cardiaque (**H**eart failure) et un âge inférieur à **75** ans. Dans un souci de simplification, afin de faciliter son utilisation en clinique, chaque critère, si présent, vaut un point avec une somme allant de 0 à 5.
L'aire sous la courbe (AUC) du score est de 0,78 (IC 95% = 0,71-0,85, p > 0,001). En analysant les sensibilités, spécificités, et valeurs prédictives positives et négatives du score, deux seuils pourraient être utiles cliniquement. Le premier permet d'exclure la présence d'un pathogène atypique si la somme du score vaut 0 ou 1, avec une sensibilité et valeur prédictive négative de 100%. Ainsi on ne manquerait aucun pathogène atypique, et on éviterait d'élargir inutilement le spectre antibiotique chez 33% des patient·e·s. Le second seuil intéressant propose d'exclure la présence d'un pathogène atypique chez les 69% des patient·e·s présentant un score de 0 à 2 ; la sensibilité est alors de 70% et la valeur prédictive négative de 98%. Ce seuil, qui présente le meilleur rapport de cotes diagnostic (DOR), permet d'être encore plus restrictif dans la prescription d'antibiotiques couvrants les pathogènes atypiques, aux dépens évidemment d'une moindre sensibilité posant le risque de ne pas traiter adéquatement certaines PAC causées par des pathogènes atypiques. Dans les deux cas, ce score pourrait être une aide précieuse afin de réduire une

prescription additionnelle d'antibiotique tout en assurant un traitement adéquat des PAC atypiques dans la majorité des cas. Il va néanmoins de soi que ce score nécessite une validation externes dans d'autres études[105].

Actuellement, des scores prédictifs similaires au score CASH-75 existent déjà. Cependant, il s'agit uniquement de scores prédisant la présence de *L. pneumophila,* laissant de côté *M.pneumoniae*. Le *Legionella score* dérivé par Fiumefreddo et coll.[51] a une AUC de 0,86 dans la publication originale et de 0,73 et 0,91 lors de validations subséquentes[56,106]. Malheureusement, notre étude n'a pas pu tenter de valider ce score, le taux de lactate déshydrogénase (LDH), un de ses critères n'étant pas disponible dans notre cohorte. Les critères du Winthrop-University Hospital (WUH) publié par Cunha et coll.[27] permettent de prédire la présence de *L. pneumophila* en utilisant 21 critères cliniques avec pondération de ceux-ci. Alors que cette publication ne donne aucune information quant à la précision de ces critères, une autre étude a décrit une AUC de 0,68 et 0,71[58]. Il existe encore deux autres scores de ce type : le score CBPIS, un score pondéré décrit par Keller et coll. (non publié) avec une AUC de 0,76[98], et le New score décrit par Saraya et coll.[97] avec une AUC de 0,62 et 0,68, mais seulement dérivé sur une cohorte de 102 patients. Malgré des recherches intensives, un score prédisant la présence d'un pathogène atypique, et non uniquement *L. pneumophila*, n'a pas été trouvé.

Ce travail a certaines forces : Il étudie une cohorte prospective et multicentrique où la recherche de pathogènes atypiques a été faite systématiquement chez tous les patient·e·s. Toutefois, il faut reconnaître certaines limites. Tout d'abord, certaines variables décrites dans la littérature comme des facteurs prédictifs n'ont pas été récoltées dans notre cohorte. De plus, un biais de classification pourrait exister avec des cas de *L. pneumophila* et *M. pneumoniae* qui n'auraient pas été proprement diagnostiqués et mal classés dans le groupe des étiologies non-atypiques, même si la recherche d'antigènes urinaires et la PCR sur frottis oropharyngé diminuent ce risque. Enfin, le nombre de patient·e·s dans le groupe des pathogènes atypiques était faible. Dans tous les cas une validation externe de ces résultats est requise.

Conclusion (français)

Certaines variables cliniques permettent de prédire la présence de bactéries atypiques comme causes d'une pneumonie acquise en communauté non sévère chez l'adulte. Le score CASH-75, dérivé à partir d'une cohorte prospective multicentrique suisse, pourrait aider à exclure la présence d'un pathogène atypique grâce à un nombre limité de critères faciles à obtenir. Son utilisation pourrait entraîner une prescription plus ciblée de l'antibiothérapie, avec de ce fait moins de pression de sélection à même d'augmenter les résistances bactériennes, moins d'effets indésirables médicamenteux et moins d'interactions médicamenteuses.

Abstract

Background

One challenge with non-severe community acquired pneumonia (CAP) is to evaluate the absence or presence of an atypical bacteria, more precisely *Legionella pneumophila* and *Mycoplasma pneumoniae*. Thus, the following dilemma needs to be solved: Is it better to broaden the antimicrobial coverage to include atypical pathogens, avoiding extrapulmonary manifestations and a potential severe course with *L. pneumophila*, or is it better to use a narrower antibiotic spectrum, hence lowering the risks of drug interactions, adverse effects, antimicrobial selection pressure and health costs? Additionally, because the microbiological diagnosis often takes time and the etiology remains unknown in most cases, the decision to cover atypical pathogens has to be made on an empiric basis, only knowing the patient's history, the results of the physical exam and a few routinely obtained ancillary tests. Thus, there is a need to establish a set of clinical features available upon admission to predict the presence of *L. pneumophila* or *M. pneumoniae* as the causative pathogen.

Methods

This work confronted the predictive factors for atypical pathogens found in a systematic literature review with those found in a population of 580 patients hospitalized for CAP between 2009 and 2013 and included in a Swiss multicentric trial. A univariate and multivariate statistical analysis were undertaken. With the established independent predictive factors, a predictive score was then derived and its accuracy was evaluated.

Results

The univariate statistical analysis showed that heart failure, confusion, high C-reactive protein (CRP) serum levels, and hyponatremia are significant positive predictive factors for atypical pathogens, while the presence of chest pain is a negative predictive factor (p-value < 0,05). Heart failure, alcohol abuse, confusion, high CRP serum levels and hyponatremia are positive predictive factors for *L. pneumophila*, yet the presence of cough and hypoxemia are negatively associated (p-value < 0,05). Both atypical pathogens and *L. pneumoniae* are more prevalent in autumnal months (p-value < 0,05). A lower leucocytes count is the only predictive factor for *M. pneumoniae* (p-value < 0,05).
In the multivariate analysis, age under 75, the presence of heart failure, the absence of chest pain, hyponatremia and contracting the disease in autumn are independent positive predictive factors for atypical pathogens. Therefore, a predictive score abbreviated in the acronym "CASH-75" was derived with an area under the curve (AUC) of 0,78 (95% CI = 0,71-0,85, p-value < 0,001). A cut-off was identified that could predict the absence of atypical pathogens with a high sensitivity and negative predictive value.

Conclusion

This study found significant predictive factors anticipating the presence of an atypical etiology, *L. pneumophila* and *M. pneumoniae*. By using the CASH-75 score, the presence of atypical bacteria could be safely excluded in a number of patients. This could enable to be more restrictive with the prescription of an additional antimicrobial in the treatment

of CAP, which could act favorably on bacterial resistance, drug adverse effects and interactions, while maintaining lower health costs.

Introduction

Background

Pneumonia is an infection of the lung parenchyma that is both common and potentially lethal. The symptoms it produces, such as cough, dyspnea or fever, are not specific and can therefore also be exhibited by other diseases. That is why the diagnosis is mainly established using a chest radiograph or another imaging modality to distinguish it from the other respiratory illnesses, both infectious or inflammatory[1]. Pneumonia can be categorized into different groups depending on the context in which the patient developed the illness. Community acquired pneumoniae (CAP) was previously defined as a pneumonia occurring less than 48 hours of hospital admission and that did not meet any criteria for healthcare-associated pneumonia (HCAP)[2,3]. The clinical use of the HCAP denomination was meant to be as a risk factor for multidrug-resistant bacteria[2], but was later demonstrated to be insufficiently accurate. Therefore, the American Thoracic Society recommended abandoning the HCAP distinction in 2019 because it lead to an increased use of broad-spectrum antimicrobials without improving the outcome of the patient[4]. Thus, pneumonia is categorized today into CAP, hospital-acquired pneumonia (HAP) with a subcategory including ventilator-associated pneumonia (VAP), and finally pneumonia in the immunocompromised host.

While pneumonia has been considered to be mainly bacterial, recent studies showed that viruses are responsible for at least 1 out of 5 cases[5,6]. Moreover, in the majority of cases a pathogen cannot be incriminated[5,7]. The most frequent bacterial cause is *Streptococcus pneumoniae* which is therefore considered as a typical pathogen, with *Haemophilus influenzae* and *Moraxella catarrhalis* among others, for their clinical manifestation is mainly confined to the lungs[8]. However the so-called atypical bacteria are also causative agents of pneumonia, such as *Mycoplasma pneumoniae, Legionella pneumophila*, *Chlamydia pneumonia* and less frequently also three zoonosis : *Chlamydia psittaci, Francisella tularensis* and *Coxiella burnetii*[8,9].

Lower respiratory tract infections, including pneumonia, are the fourth most frequent cause of death and the second most common cause of years of life lost worldwide[10]. In Europe and the USA, CAP is the most common cause of death due to an infection[11]. In Europe, CAP has an incidence of 1,07 to 1,2 per 1000 person-years, that increases up to 14 per 1000 person-years in the population over 65 years old[12]. In Switzerland, a total of 22'928 hospitalization due to pneumonia have been recorded in 2019[13]. Because CAP mainly affects the older age groups and the population tends to age, an increase of hospital admissions for this disease is expected in the years to come[11,12].

The main risk factors for CAP can be classified into three categories : constitutional, with older age and male sex; occupational, such as smoking, alcohol abuse and contact with children; and finally related to comorbid conditions, with poor nutritional state, poor dental hygiene, chronic respiratory and cardiovascular disease, Parkinson's disease, epilepsy, dementia, dysphagia, and chronic liver or kidney disease[12].

Atypical pathogens

Historically, the distinction between typical and atypical pneumonia was meant to be clinical, the latter causing extrapulmonary manifestations, such as meningoencephalitis, pericarditis, myocarditis or gastrointestinal involvement (e.g. watery diarrhea), that could be interpreted as syndromes[8,14]. However, it is now clear that in practice this

discrimination is not possible from a clinical and radiological standpoint[15,16]. Nowadays the distinction between typical and atypical bacteria is centered around one main aspect from a microbiological point of view: the intracellularity of atypical pathogens. This consequently makes them resistant to the conventional antimicrobial therapy used to treat *S. pneumoniae*[17], while responding to macrolides, tetracyclines and fluoroquinolones[14]. Yet this categorization remains useful when it comes to discussing the empirical treatment of pneumonia. Even though the antibiotics used against atypical pathogens are also working against typical bacteria, they are nevertheless not the therapy of first choice, because they either favor the appearance of multiresistant bacteria (fluoroquinolones), or typical pathogens already are resistant against them (macrolides and tetracyclines)[14].

The overall prevalence of CAP caused by an atypical bacteria among adults is 14%[18], with wide variations between studies. While atypical pathogens are classically considered to be mainly infecting children and young adults, Lui et al.[19] showed that they are present in 11,2% of all pneumonia in adults and 28,6% when a causative microbe was identified. They can also infect the elderly, as Maruyama et al.[20] demonstrated in their study, observing that atypical pathogens were found in 44,7% of CAP in patients 85 years and older. Nevertheless, this result other studies describe a lower prevalence, for example one where the prevalence of atypical pathogens was 2% in patients 80 years and older[21], and a meta-analysis where the prevalence of *L. pneumophila* in the elderly ranges from 0 to 15%[22].

Chlamydia pneumoniae has been identified as a common cause of pneumonia in older studies based on serology, with a prevalence estimated at 10%[23]. However, recent studies, where the diagnosis was made using polymerase chain reaction (PCR), found a much lower prevalence, of less than 1% [24,25]. This gainsays the apparent high prevalence described previously in serological studies, the increasing seroprevalence with age[26] not being synonymous with being the causative agent of pneumonia. In general, all zoonotic pneumonias – *C. burnetii, F. tularensis* and *C. psittaci* – can be reasonably excluded from the differential diagnosis by a thorough patient history, taking animal exposure into account[8,27,28], and therefore we will not focus on these pathogens. Thus, the present study will focus on two major atypical pathogens: *L. pneumophila* and *M. pneumoniae.*

Legionella pneumophila

L. pneumophila was first described following the 1976 Philadelphia outbreak at the American Legion convention[29]. It is an obligate aerobic, nonfermenting, facultative intracellular, gram-negative bacilli[29–31]. The bacteria contaminates fresh water sources living in amoebas, making up a biofilm in stagnant water with a temperature ranging from 20 to 70°C. In the human body, it settles into macrophages from the respiratory tract[27,31–33]. The infection route is therefore only via a direct contact with a contaminated environment or through aerosols from this same source (e.g. from cooling towers, whirlpools…), and never from person to person[32,34–37]. If the source is not controlled, an epidemic could break out[38–40], and that is one of the reasons why Switzerland has a mandatory declaration of *L. pneumophila*[41]. This bacteria is more common in summer and early fall with warm and humid weather[42–45]. Moreover, this period coincides with travelling for vacations, 1 legionellosis out of 5 being associated with travel. This phenomenon has two aspects to it : contracting the disease while traveling to a place where there is a contaminated water source and contracting the disease when returning

home, where the water became stagnant during the traveling period[31]. The incubation period ranges from 2 to 10 days[31].

L. pneumophila mostly infects the elderly, sparing the young adults and being extremely rare among children[18,36,45,46]. Worldwide this pathogen is responsible for 3% of pneumonia[18] and in Switzerland an average of 376 cases per year have been declared from 2010 to 2019 with a constant increase of incidence in the last two decades[47]. The surge in incidence could be explained by a better recognition of the cases, the aging population and climate change provoking higher temperatures with stronger rainfalls[31].

L. pneumophila is the third most frequent pathogen incriminated in severe CAP[48], making this bacteria an independent risk factor for severe CAP[48], and has a mortality rate between 10 and 20% [46,49–52]. As extrapulmonary manifestations, it can also specifically cause hepatitis and renal disease[8,14]. Moreover Legionnaire's disease is commonly described as a syndrome[53], each sign alone not being pathognomonic, but the constellation of all signs and symptoms put together becoming more specific[27]. In some patients, *L. pneumophila* can also cause the so called Pontiac fever, which is a non-severe flu-like syndrome without pneumonia and that does not necessarily need an antimicrobial therapy[31].

From a diagnostic point of view, the presence of *L. pneumophila* is mainly proven by detection of urinary antigens. This diagnostic test has a specificity around 99%[31] and a sensitivity ranging between 56 and 99%[45]. Since it only detects serogroup 1 (approximately only 70-80% of all serogroups), a negative test cannot rule out with certainty the presence of this pathogen[8,14,31,54], especially if the disease is mild[16]. Moreover, even though it remains positive for weeks[8], the urinary antigen test may need a few days to become positive[27,55–58]. Detection of *L. pneumophila* in respiratory samples can be done using culture on special mediums or through nucleic-acid detection techniques (PCR). However, these samples can be hard to collect, because *L. pneumophila* mainly causes a dry, non-productive cough[31,58]. A serology is not useful, since the seroconversion only happens 6 to 8 weeks after the infection and could remain positive during years[31]. Direct immunofluorescence is not used either, having a too low sensitivity[31].

The treatment options for *L. pneumophila* are respiratory fluoroquinolones such as moxifloxacin and levofloxacin, macrolides like azithromycin and clarithromycin, and doxycycline[31]. This bacteria is intrinsically resistant to beta-lactam antibiotics being an intracellular bacteria[59] and having a beta-lactam-inactivating action[60].

Mycoplasma pneumoniae

M. pneumoniae was first discovered by Eaton et al. in 1944 and was therefore first called the Eaton agent[61]. It is a small bacteria that lacks a cell wall[30,61,62] with a small genome, that does not contain any genes coding for a bacterial wall[63], and restricted metabolic capacities, consequently depending on a parasitic intracellular life existence[61]. Its filamentous form adheres to the respiratory epithelium[32] and once it starts its intracellular life, the host cell protects the bacteria from the mucociliary system[61]. The pathogen is transmitted via aerosolized droplets from person to person[36], especially in closed populations (e.g. military bases, care facilities…) where attack rates ranging from 25 to 71% have been reported[61]. This bacteria is endemic throughout the year, with a higher relative prevalence during summer, since other respiratory viruses are less frequent[61], and causing occasional epidemics every 4 to 6 years[18,32,64–66]. The incubation period typically lasts between 1 and 3 weeks[61].

M. pneumoniae usually affects adolescents and younger adults[67,68], but still causes pneumonia in older age groups[69,70]. This bacteria accounts for 7% of all pneumonia globally[18] and in Switzerland 463 patients were hospitalized for a pneumonia caused by this pathogen in 2019[13].
M. pneumoniae more frequently causes a mild and self-limiting CAP that can often be treated without hospitalization, and is therefore often referred to as a "walking pneumonia"[14,32,61]. Besides the pulmonary symptoms, it specifically causes dermatological disorders[8,32,64], Guillain-Barré Syndrome[32,71,72] and hematological disorders (e.g. cold agglutinins)[32,64]. *M. pneumoniae* is also linked with upper respiratory tract manifestations and incriminated for exacerbating or even causing asthma[8] through the release of pro-inflammatory cytokines[61]. In animal models a potentiating role for *S. pneumoniae* was also described[14].
The most common diagnostic tool is a PCR of the sputum or a nasopharyngeal swab. Moreover a recent study on a pediatric population suggested that a PCR of the upper respiratory tract can in fact not differentiate between an infection or just a simple carriage of this pathogen[73]. Culture is also possible, but fastidious and rarely done[64]. A serological diagnosis could be made if the immunoglobulins M (IgM) levels are increased, but an increased immunoglobulins G (IgG) level would only indicate a past infection[8].
For *M. pneumoniae* the effective treatment possibilities are the following: respiratory fluoroquinolones, tetracyclines, such as doxycycline and minocycline, and macrolides. The later are especially useful in children where the two other groups are relatively contraindicated[74]. Again, beta-lactams are not a successful option because they act on the bacterial cellular wall that *M. pneumoniae* happens to lack[64].

Current treatment guidelines for CAP

Form a therapeutic standpoint, several different guidelines exist. All agree to use a combination of a beta-lactam with an antibiotic covering atypical pathogens as the treatment of severe CAP, typically in patients admitted to the intensive care unit. The guidelines concerning moderately severe CAP, typically in patients hospitalized in non-intensive stations, are, however, more divers.
According to the German, Austrian and Swiss common "S3-guidelines"[75] for hospitalized patients with severe CAP, the antimicrobial therapy is composed of a large spectrum beta-lactam and a macrolide, because there is the need to cover all possible causative pathogens – typical and atypical – and macrolide might also be beneficial for its immunomodulatory action[76]. However, when it comes to non-severe CAP, the choice is up to the physician, whether a macrolide should be added to the beta-lactam regimen or not. Without a macrolide, atypical bacteria will not be covered by the beta-lactam regimen alone because of their intrinsic resistance[19].
The guidelines from the European Respiratory Society[77] also recommend the empiric use of a beta-lactam more or less a macrolide for hospitalized patients with no need of intensive care treatment. They also recommend the use of a combination therapy mainly in higher risk patients. The American Thoracic Society guidelines[4] recommend, as the empiric treatment for non-severe cases, a bi-therapy with a beta-lactam and a macrolide or a mono-therapy with a respiratory fluoroquinolone (levofloxacin or moxifloxacin).
Then why not cover systematically atypical pathogens in all patients with pneumonia? The short answer is drug interactions, adverse effects, antimicrobial selection pressure causing bacterial resistance and higher costs[78].

By adding a macrolide, the patient risks drug interaction through its inhibitory action on the CYP3A4 and therefore interacting with other drugs being metabolized by this enzyme complex [79,80]. Nevertheless, unlike clarithromycin or erythromycin, azithromycin does not interact with CYP3A4[80]. Other pharmacokinetic drug interactions are also possible via an increased gastric emptying and the antimicrobial effect on the gut flora (as any other antimicrobial drug)[80]. Gastrointestinal side effects are the most frequent, especially with erythromycin[81]. Macrolides have also been linked to cardiovascular events such as acute coronary syndrome and QT interval prolongation, notably with erythromycin[55,82]. Nevertheless they still have a relatively safe profile and have been therefore prescribed widely, representing 10 to 15% of the global oral antimicrobial market[81]. This unfortunately promoted an increased bacterial resistance[56,64,78], both on an individual and community scale. This latter is especially alarming for *M. pneumoniae*[83,84], macrolide resistance reaching as high as 95% in some parts of China[74], which has a direct negative impact on the severity of the disease[64]. In Europe, resistance to macrolides seems less frequent, especially in adults where it has been described as a sporadic issue, with a prevalence of resistant *M. pneumoniae* ranging between 1,3% of all CAP in Italy[85] and 3,1% in Germany[68]. However there is also a lack of thorough monitoring in Europe, which could lead to an underestimation of the extent of the problem[86].

Respiratory fluoroquinolones commonly cause mild side effects such as gastrointestinal disturbances and headaches, while other are uncommon but more serious like QT interval prolongation, tendon rupture, glucose homeostasis dysregulation, renal damage or seizure[87]. The QT prolongation is besides a source of concern with potential interaction with other drugs. Fluoroquinolones also have a toxic effect on growth cartilage and are therefore contraindicated in children, as well as during pregnancy and breastfeeding[88,89]. With its large action spectrum, especially levofloxacin's and moxifloxacine's action on Gram positive pathogens, and the good oral biodisponibility, fluoroquinolones have been widely prescribed for a range of indications. This use has been directly correlated to the emergence of multidrug resistant bacteria (MDR), such as extended spectrum beta-lactamase (ESBL) producing enterobacteria and methicillin-resistant *Staphylococcus aureus* (MRSA)[90,91]. They are also linked to causing iatrogenic pseudomembranous colitis by *Clostridioides difficile*[91,92]. It is important to note that most antimicrobial agents can lead to *C. difficile* infections.

Tetracyclines can commonly cause anorexia, gastrointestinal manifestations, rash and photosensitivity[74]. They also cause teeth discoloration in children and are hence contraindicated in children younger than eight[93]. While resistance to fluoroquinolones and tetracyclines in *L. pneumophila* and *M. pneumoniae* are not an actual problem from a public health standpoint[84], some cases of resistance have already been described[94,95] and one cannot exclude that this might become an issue in the future.

Predicting the presence of atypical pathogens

Thus, there is a dilemma between covering atypical pathogens in order to avoid extrapulmonary manifestations and the potential severe outcome of a *L. pneumophila* pneumonia, and adding unnecessarily another antimicrobial that could beget adverse effects and bacterial resistance. This speaks in favor of finding an efficient way to clinically detect CAP caused by atypical pathogens. This way the empirical treatment could be shortly begun while still being as targeted as possible, only covering atypical pathogens if necessary.

The main issue here is that the therapeutic decision must be taken rapidly in order to start the correct antimicrobial therapy as soon as the pneumonia has been diagnosed[77]. Unfortunately, in a clinical setting a microbiological diagnosis is not usually made in this time interval[58] and the antimicrobial therapy is therefore empirically begun[17]. Moreover, with more than half of all pneumoniae not having a proven microbiological etiology, the antibiotic treatment often remains empirical until the end[5,7]. Thus, there is a big interest in developing a clinical score able to predict the presence of atypical pathogens[96] based on the patient's demographic, comorbidities, symptoms, clinical exam and complementary exams upon arrival at the hospital. If a such score could be both discriminative and easily used in practice, less time would be wasted waiting a microbiological result, the antimicrobial therapy would be adequate, and a cost reduction could even be considered. Hence, the present work asks the following question: **In immunocompetent adult patients hospitalized for a non-severe community-acquired pneumonia, which clinical characteristics available upon hospital admission can predict the presence of *Legionella pneumophila* or *Mycoplasma pneumoniae* as the causative pathogen?** We hypothesize that there are well described predictive factors in the literature and that these characteristics are also predictive for the presence of *L. pneumophila* and *M. pneumoniae* in a Swiss contemporary population. Moreover, we also hypothesize that some predictive factors can be rationally used in clinical practice to streamline empiric antibiotic therapy.

Methods

Literature review

Before trying to identify predictive factors in a swiss contemporary population, we conducted a systematic review on the topic. The literature search was done in the *PubMed* data base using the following equation:

```
(((("Pneumonia"[Mesh] NOT "Healthcare-Associated Pneumonia"[Mesh]) AND ("Mycoplasma pneumoniae"[Mesh] OR "Legionella pneumophila"[Mesh])) OR ("Pneumonia, Mycoplasma"[Mesh] OR "Legionnaires' Disease"[Mesh])) AND ("Epidemiology"[Mesh] OR "Risk Factors"[Mesh] OR "Protective Factors"[Mesh]) NOT ("Pediatrics"[Mesh] OR "Immunocompromised Host"[Mesh])
```

The search retrieved 397 results; after screening titles, abstracts and full texts using the PRISMA method[107], a total of 42 articles were kept. An additional 22 articles were identified through a review of the references lists. They listed precisely predictive and risk factors, both negative and positive, for pneumonia in adults caused by either atypical pathogens, or *M. pneumoniae* and *L. pneumoniae* alone. Only factors with a p-value inferior to 0,05 were taken into consideration. Figure 1 summarizes the process of selection.

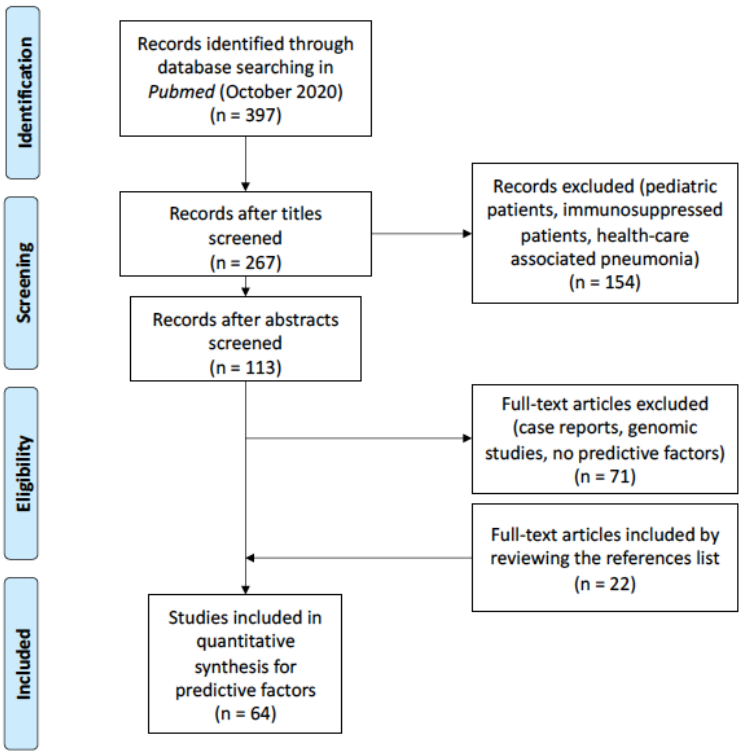

Figure 1 - Flowchart with the PRISMA method

Population

We conducted a secondary analysis of the data collected in the BICAP database[108,109]. The latter is a swiss multicentric prospective data base with adult patients hospitalized for a CAP from 2009 to 2013, used initially to compare the mono-antimicrobial therapy (cefuroxime or amoxicillin alone) with a bi-therapy (cefuroxime or amoxicillin, plus clarithromycin). All patients gave their written informed consent, their data were de-identified, and the study was approved by the competent ethics committee.

In order to be included, patients had to show at least 2 clinical signs of pneumonia and needed a lung infiltrate demonstrated on a conventional chest radiography. Patients were excluded if they had any form of severe immunosuppression, were hospitalized in the last 14 day, resided in nursing homes, had received an antibiotic in the last 48h or if their pneumonia was considered severe (Pneumonia Severity Index (PSI) category V).

Upon arrival, 2 pairs of hemocultures, a urine sample for the detection of antigens for *L. pneumophila*, and oropharyngeal swabs for the detection of *C. pneumoniae* and *M. pneumoniae* by PCR were obtained for all patients. Some patients also had urinary antigens for *S. pneumoniae* tested. Sputum were obtained for culture in all patients able to expectorate, and pleural fluid was sampled for culture according to recommendations.

Univariate statistical analysis

Patients from the BICAP data base were separated in 2 main groups: pneumonia caused by atypical pathogens (thereafter called “AP”) and all other pneumoniae (“NAP”). The AP were further divided into two smaller groups: pneumonia caused by *L. pneumophila* called “LP” and pneumoniae caused by *M. pneumoniae* called “MP”. Figure 2 summarizes the different groups.

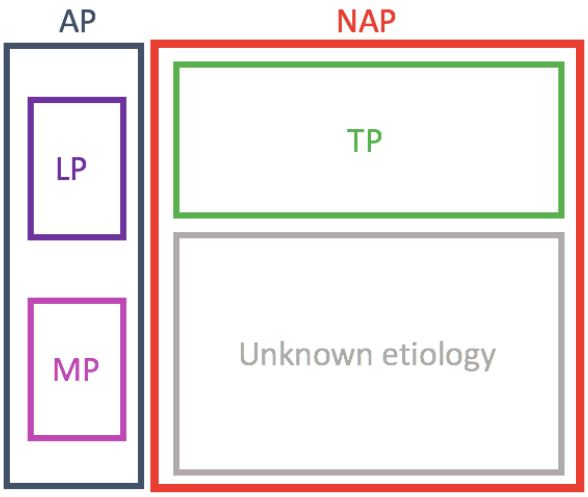

Figure 2 - Groups used for the statistical analysis (AP = atypical pathogens, LP = Legionella pneumophila, MP = Mycoplasma pneumoniae, NAP = non atypical pathogens, TP = typical pathogens)

The univariate analysis compared in first place the AP group with the NAP group, and in a second place, both the LP and MP groups were independently compared to all other patients; i.e the LP group was compared to the sum of NAP and MP group, and vice-versa. All the same, we need to assume that some unknown etiology cases are misclassified and that they should indeed be assigned to the AP group. In other words, the NAP group probably consists of a few AP cases, causing some measurement biases. However, these comparisons (AP vs. NAP, LP vs. NAP + MP, and MP vs. NAP + LP) are intended to be similar to the clinical practice, where the etiology remains mostly unknown. As the intention of our study is to uncover predictive factors in an everyday practice, this methodology appears to be the most relevant.
All statistics were done using the SPSS software (IBM). Descriptive data used frequencies with percentages, means with standard deviations (normal distribution) or median with interquartile range (skewed distribution). Categorical data was compared between groups with Chi square or Fischer's exact test as appropriate. Continuous data was compared with an analysis of variance (ANOVA). A p-value of 0,05 or less was considered significant.

Multivariate statistical analysis

Once the univariate analysis was done, predictive factors associated with the dependent variable with a p value <0,1 were entered in a multivariate logistic regression model, using backward conditional regression. For the comparison between the AP and NAP groups, because the number of patients is equal to 31, a maximum of 6 variables were accepted in the final model (one for every five patients).

Elaboration of a predictive score

With the variables that were proven to be independent predictive factors in the multivariate analysis, a predictive score was elaborated. All variables were dichotomized in order to be simply used in an everyday clinical setting. While the binomial categorical variables (absence or presence of a certain characteristic) needed no further transformation, continuous variables had a threshold established and were this way

dichotomized. This cut-off was selected using the receiver operating characteristic (ROC) curve and the Youden Index[110].

Each clinical condition was awarded 1 point if present and the score's result was the sum of all points. The performance of the score was materialized by a ROC curve and for each possible cut-off, the sensibility, specificity, positive and negative predictive value, positive and negative likelihood ratio, and diagnostic odds-ratio (DOR)[111] were computed. With all this tools in hand, the best cut-off could be established. Because the main aim of this score was to exclude an atypical bacteria as the etiological pathogen, the threshold with a high sensitivity and a high negative predictive value was sought, to the detriment of a lower specificity.

Results

Literature review

Scanning through the 64 articles included in our systematic review of the literature, a certain number of predictive factors – both positive and negative for the presence of atypical pathogens – were uncovered. While some studies pointed out risk factors for the presence of atypical pathogens, not specifying which one, most focused on either *L. pneumophila* or *M. pneumoniae.* Table 1 summarizes all predictive factors with the color code as follows: grey for demographical factors, dark blue for symptoms, red for clinical signs, orange for vital signs, green for ancillary tests (laboratory and chest radiography), yellow for scores, light blue for comorbidities and finally purple for exposure factors. It is important to note that some predictive factors have been described as positive in some studies and negative in others, contradicting each other.

Results

Table 1 - Summary of all predictive factors described in the literature review (Na^+ = sodium, Hb = hemoglobin, COPD = chronic obstructive pulmonary disease, BUN = blood urea nitrogen, PCT = procalcitonin, LDH = lactate dehydrogenase, CK = creatinine kinase, AST = aspartate transaminase, GPT = glutamic pyruvate transaminase, CXR = chest X-ray) (color coding : grey = demographical factors, dark blue = symptoms, red = clinical signs, orange = vital signs, green = ancillary tests (laboratory and chest radiography), yellow = scores, light blue = comorbidities, purple = exposure factors)

Bacteria	Positive predictive factors	Negative predictive factors
Atypical pathogens	Age < 65[19]	
	Female[19]	
	Diarrhea[112]	
	Fever ≥ 38,0°C[19]	
	RR < 25/min[19]	
	Na^+ > 130 mEq/L[19]	
	Leucocytes < 11.10^9/L[19]	
	Hb < 11 g/dL[19]	
		COPD[112]
Legionella pneumophila	Age > 50[45,46] or > 65[113]	Older age[98,102,114] or age > 60[99]
	Male[43,46,97–100,115]	
		Cough[51,98–100,115,116]
		Sputum[51,52,57,98–100,106,114,116]
		Pleuritic chest pain[52,58,98–100,102]
		Upper respiratory symptoms (rhinitis or sore throat)[52]
	Dyspnea[115,116]	Dyspnea[51,102]
	Diarrhea[57,98,106,112], nausea[106] or gastro-intestinal symptoms[52,98]	
	Lethargy[58]	
	Headache[16,52,98–100]	
	Arthralgia[100,102] or myalgia[98,100,102]	
	Confusion[52,57,98,116–119]	
	Prodromal toxic illness[118]	
		Normal chest auscultation[57]
		Pleural effusion[100,102]
	Multilobular pneumonia[100]	
	Disparity between physical and radiological findings[98]	
	Temperature > 40°C[57,112], > 39,4[56], > 39[16,98], > 38,9°C[119], > 38,3[106] or elevated[51,97,99,100,106,114]	
	Heart rate > 90/min[57] or tachycardia[97]	
	Respiratory rate > 30/min[117]	
	Relative bradycardia (increase < 10 bpm/increase of 1°C)[54,97,114]	
	Need for mechanical ventilation[117,120] or respiratory failure[52,120]	
		Blood pressure decreased (systolic and diastolic)[114]
		Lower body weight[114]
	CRP > 200 mg/L[57], > 187[56], > 210[97] or elevated[51,54,97,106,115,116]	
	Creatinine > 90 µmol/L[57], > 2,0 mg/dL[120] or increased[52,116]	
	Na^+ < 130 mEq/L[16,57,99,100,118,120], < 133[56], < 137[97] or decreased[51,97,98,115,116,119,121–123]	
	BUN ≥ 30 mg/dL[120]	
	PCT elevated[56,106] or Increase in neopterin > increase in PCT[124]	

	LDH elevated[51,97,98,115,116,121], > 700 U/L[16] or > 292 IU/L[97]	
	CK > 232 U/L[99] or elevated[51]	
	Liver enzymes elevated[51,52,97,116,118,125], transaminases > 40 U/L[100], AST > 37 U/L[99] , > 40 U/L[126] or elevated[121], GPT increased[102]	
	Acidosis[51,117] or pH ≤ 7,35[120]	
	Hypoxia[117]	
	Iron overload[46]	
	Total protein decreased[121]	
	Albumin > 30 g/L[100] or decreased[106,121]	
	IgG decreased[121]	
	Platelet < 171 G/L[56] or decreased[51,114]	
	Neutrophilia[106] or neutrophil:lymphocytes elevated[106]	
		Leucocytes > 12 G/L[100] or > 10 G/L[118]
	Microscopic hematuria[58,126] or hemoglobinuria[51]	
	Proteinuria[51]	
	CXR infiltrate[57]	
	CXR infiltrate progression to another lobe[52,126] or extension[118]	
		CXR effusion[57,102]
	CURB-65 ≥ 3[57]	
	SOFA ≥ 7[120]	
	APACHE II score ≥ 14[120]	
	Shock[120]	
	Sepsis[57]	
	WUH point score[58] or WUH modified > 5[8]	
	Legionella score by Fiumefreddo ≥ 2[51,56,106] or ≥ 4[97]	
	Saraya score≥ 3[97]	
		Legionella score by Fiumefreddo <2[51,56,106]
		WUH modified < 5[8]
		Septic shock[98,100]
		High risk PSI (IV and V)[100]
	Chronic lung disease[45,46,49,101,104,123,127], COPD[43,54,58,102,113,123,128], previous bronchitis[34] or silicosis[129]	COPD[51,56,98–100]
	Cardiac disease[101,104]	Chronic heart failure[56] or heart disease[51]
	Diabetes mellitus[42,45,46,104,113,130]	
	Hepatitis C or end stage liver disease[113]	Liver cirrhosis[56]
	End stage renal disease[130]	
	Non cutaneous neoplasm[131] or cancer[49,130]	
		Chronic cognitive deficit[100]
	Smoking[34,34,43,45,46,49,52,98,100–102,104,115–117,123,127–136]	
	Alcohol abuse[46,49,52,98–100,127]	
		Intra-venous drug use[56]
	Previous pneumonia[34] or admission du to pneumonia in the previous year[101]	Previous pneumonia[99] or previous URTI[98,126]
	Previous antibiotic therapy[52,98,137] or previous ß-lactam therapy[98,100,102]	Previous antibiotic therapy[99]
		Influenza vaccine[100] or Pneumococcal vaccine[100]

	Rainfall[44,138], warm weather[42,139], high humidity[139] or summer[130]	
	Poverty[43]	
	Work in transportation[140,141], repair, protective services, cleaning services or construction[43]	
	Recent travel[46,57,100,131,133,142], hotel stay[54,133]	
	Cruise ship, sauna or hot tub in the previous 2 wk[54]	
	Wash basin for personal hygiene[133]	
	Home ownership[133]	
	Gardening or spraying house plants[133]	
	Use of pressurized water[133]	
	Proximity to a cooling tower[104,129,136,143–147]	
	Private water supply, plumbing work or electric water heater[135]	
	Exposure to a plume of smoke[148]	
	Work > 40 h/wk[135]	
	Spending > 100 min/d outside[129]	
Mycoplasma pneumoniae	Younger age[67,68]	
	Female[67,68]	
	Relative bradycardia (increase < 10 bpm/1°C increase)[54]	
		Confusion[67]
		Pleural effusion[67]
		Oxygen requirement[67]
	Lower CRB-65 (≤ 2)[67] or lower CURB-65 (≤ 1)[68]	
	Cold agglutinin titer > 1:64[8]	
		CRP elevated[67]
		Leucocytosis[67]
		High levels of IgG for *M. pneumoniae*[149]
	COPD[54]	Chronic respiratory disease[67,68]
		Congestive heart failure[67]
		Renal insufficiency[67] or chronic renal disease[68]
		Diabetes mellitus[67]
		Neoplasm[67]
	Smoking[149]	
	Previous antibiotic therapy[68]	

Clinical scores already existing

A few predictive scores for *L. pneumophila* have been described, yet unlike the CURB-65[150] that is easy to remember and use, the WUH Criteria[36,58,116], the Legionella Score[51,56,106,115,116], the CBPIS score[21,116] and the scoring system by Saraya et al.[97] are all difficult to remember with the various cut-offs and therefore not commonly used in practice. For *M. pneumoniae* no such score has been described to our knowledge so far.

The Legionella Score was first described by Fiumefreddo et al.[51] and published in 2009. The Swiss derivation cohort comprised 450 pneumonia patients; 82 of them being caused by *L. pneumophila*. A univariate followed by a multivariate analysis were made and 6 variables were found to be independent predictive factors: two clinical, body temperature and the absence of sputum, and 4 laboratory values, sodium, lactate dehydrogenase (LDH), C-reactive protein (CRP) and platelet count. Each independent factor was then

dichotomized with the optimal cut-off (p-value < 0,0001) and they were assembled in a score, with each variable being worth one point. The receiver operating characteristic (ROC) and the area under the curve (AUC) were all calculated for the 6 dichotomic variables and the score. Table 2 summarizes the score and statistical characteristics. The optimal cut-off for this score was considered to be 2 and was meant to exclude the presence of *L. pneumophila* if the score is equal to 0 or 1.

Table 2 - Characteristics of the Legionella score as derived by Fiumefreddo et al. (Sensi = sensitivity, Spe = specificity, AUC = area under the curve, CI = confidence interval)

Variable	AUC (95% CI)	Optimal cut-off	Sensi (%)	Spe (%)	P-value
Temperature	0,74 (0,63-0,78)	> 39,4°C	48,1	84,4	< 0,0001
No sputum	0,68 (0,61-0,74)				< 0,0001
Sodium	0,71 (0,63-0,78)	< 133	64,6	70,8	< 0,0001
LDH	0,62 (0,53-0,71)	> 225	67,1	58,1	< 0,0001
CRP	0,78 (0,70-0,82)	> 187	71,6	64,7	< 0,0001
Platelet count	0,71 (0,64-0,78)	< 171	45,7	83,6	< 0,0001
Score	0,86 (0,81-0,90)	≥ 2	78,0	78,8	

Several publications have externally validated this score on different cohorts, using a cut-off of 2, as previously described. Table 3 recapitulates these publications.

Table 3 - Validation studies for the Legionella score (CAPO = Community Acquired Pneumonia Organization)

Authors	Date of publication	Geographic location of the cohort	Total number of patients	Total of *L. pneumophila* cases	AUC (95% CI)	Sensi (%)	Spe (%)
Haubitz et al.[56]	2014	International database (CAPO)	1939	37	0,73 (0,65-0,81)		
Miyashita et al.[115,116]	2017 and 2018	Japan	595	176		94,3	48,9
Bolliger et al.[106]	2019	Switzerland	713	33	0,91 (0,86-0,96)		

An additional study by Saraya et al.[97] published in 2018 about a cohort of 102 patients in Japan, 34 amongst them being positive to *L. pneumophila,* only described the AUC using cut-offs of 4 and 5. It is also important to take into account that this study used as control cases only pneumonia caused by *S. pneumoniae.* Table 4 gives an insight at the results.

Table 4 - Validation study for the Legionella score by Saraya et al.

Variable	Cut-off	Sensi (%)	Spe (%)	AUC (95% CI)	P-value
Score	≥ 4	47,1	95,6	0,713 (0,587-0,830)	< 0,001
Score	≥ 5	17,6	97,1	0,574 (0,451-0,696)	0,0228

The Winthrop-University Hospital (WUH) Criteria were described by Cunha et al.[27] in 1998. A score was developed using 3 confirmed cases of pneumonia caused by *L. pneumophila* published in the clinical pathologic conferences pages from the New England Journal of

Medicine (NEJM), yet no control cases were used, and no statistical analysis was made. If the sum of all points was below 5, the diagnosis of *L. pneumophilia* was unlikely, while being between 5 and 10 made it probable and above 10 highly probable.

Table 5 - The WUH scoring system

Criteria	**Points**
Headache	1
Confusion/encephalopathy	2
Lethargy	3
Ear pain	-3
Non-productive cough/sore throat	-3
Hoarseness	-3
Purulent sputum	2
Mild-to-moderate hemoptysis	-1
Pleuritic chest pain	-2
Loose stool/diarrhea	3
Abdominal pain w/ diarrhea	5
Abdominal pain with diarrhea	5
Relative bradycardia	5
Acute renal failure	5
Hyponatremia	1
Hypophosphatemia	4
Increased serum transaminases	4
Increased total serum bilirubin	2
Increased cold agglutinin titer	-3
Increased creatinine	1
Microscopic hematuria	2

Two validation studies were published to our knowledge, giving some statistical weight to the WUH Criteria. They are summarized in Table 6. Gupta et al.[58] tested the score twice: once using all patients included even if they had missing data, and a second time using only the patients were the data set was complete, i.e. all criteria could be tested.

Table 6 - Validation studies for the WUH Criteria

Authors	Date of publication	Geographic location of the cohort	Total number of patients	Total of L. pneumophila cases	Cut-off used	AUC (95% CI)	Sensi (%)	Spe (%)
Gupta et al.[58]	2001	USA	68	37	≥ 5	0,72 (0,66-0,78)	91,9	31,2
					≥10	0,72 (0,66-0,78)	78,4	64,5
			41	23	≥ 5	0,68 (0,59-0,77)	91,3	22,2
					≥10	0,68 (0,59-0,77)	86,9	50,0
Miyashita et al.[116]	2017	Japan	595	176	≥ 5		89,8	53,5
					≥10		70,4	82,3

The Community-based Pneumonia incidence Study Group Legionella Scoring System (CBPIS) was first described by Keller et al. at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy in 1995 in abstract form, but it was never published in a peer-reviewed journal, and we were unable to obtain an electronic archive from the abstract. However, this score has been used in two subsequent studies for validation. The score is described by Table 7. If the sum of the score is 4 or lower, it means the probability of the pneumonia being caused by *L. pneumophila* is low, between 5 and 9 is moderate and 10 or higher is high.

Table 7 - CBPIS score

Variable	Cut-off	Points
Maximum temperature in 24h (°C)	< 37,8	0
	37,8 – < 38,3	1
	38,3 – < 38,9	2
	38,9 – < 39,4	3
	39,4 – < 40	4
	≥ 40	5
Serum creatinine concentration (md/dL)	< 1	0
	≥ 1	1
Serum sodium concentration (mmol/L)	≥ 140	0
	135 – < 140	1
	130 – < 135	2
	< 130	3
Serum LDH concentration (U/L)	> 250	0
	250 – < 500	1
	≥ 500	2
Headache	No	0
	Yes	2
Vomiting	No	0
	Yes	2
Smoking within 1 month of illness onset	No	0
	Yes	2

Two studies were published to date in an effort to validate this score. All their characteristics are shown is Table 8. It is important to note that the study from Fernández-Sabé et al.[98] only used *S. pneumoniae* pneumonia as control cases.

Table 8 - Validation studies of the CBPIS score

Authors	Date of publication	Geographic location of the cohort	Total number of patients	Total of L. pneumophila cases	Cut-off used	AUC	Sensi (%)	Spe (%)
Fernández-Sabé et al.[98]	2003	USA	207	78	≥ 5	0,76	96,1	17,0
					≥10	0,76	51,3	86,0
Miyashita et al.[116]	2017	Japan	595	176	≥ 5		88,6	34,8
					≥10		32,4	94,5

The scoring system by Saraya et al.[97] was derivated from a cohort of 102 patients in Japan, with 34 of them having *L. pneumophila.* The *L. pneumophila* cases were only compared to *S. pneumoniae* cases. The score is based on 4 independent predictive factors that have been dichotomized with each being worth 1 point if present (see Table 9). The cut-off was seen as promising with a score equaling 3 or 4. No validation studies have been published to date.

Table 9 - Scoring system by Saraya et al.

Variable	Cut-off	AUC (CI 95%)	Sensi (%)	Spe (%)
Relative bradycardia				
LDH	≥ 292 IU/L	0,810		
CRP	≥ 21 mg/dL	0,892		
Sodium	≤ 137 mmol/L	0,780		
Score	≥ 3	0,682 (0,558-0,806)	36,3	100
	≥ 4	0,627 (0,501-0,754)	27,35	98,2

When comparing AUC in this study, it seems that using the LDH, CRP or serum sodium levels alone have a better predictive value for the presence of *L. pneumophila* than the score itself, which questions the usefulness of this score. This could be explained by the low number of patients in this cohort. Nevertheless, validation studies are needed for this score.

Population used for the univariate and multivariate analysis

602 patients were first included in the BICAP cohort, but eventually 22 were excluded, leaving a total of 580 patients. The cohort had an average age of 76, ranging from 21 to 101, and an average PSI score of 84. Atypical pathogens were diagnosed in 31 patients: 16 with *L. pneumophila* and 15 with *M. pneumoniae*. No patient was diagnosed with *C. pneumoniae*. The NAP group was composed of 549 patients with 149 having a proven etiology (88 *S. pneumoniae* and 61 other bacteria) and 400 with an etiology that remains unknown, despite all microbiological diagnostic tests done.

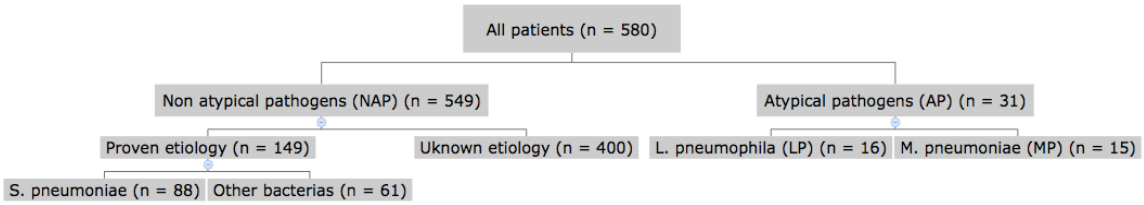

Figure 3 - Etiologies of pneumonia in the BICAP cohort

Univariate statistical analysis

Demographical factors

As demographic factors, we only tested age and gender and, in our cohort, there is no significant difference between etiological groups for these criteria, though there was a trend towards a younger age being associated with the AP group. While for *M. pneumophila* being younger and female was a risk factor in the literature and while for *L. pneumophila* being older than 50 and male was a positive predictive factor, none of these trends can be found here.

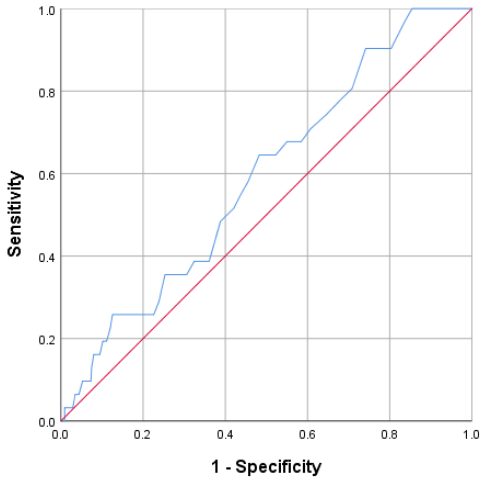

Figure 4 - ROC curve for age (decreasing), for AP vs. NAP. AUC = 0,59 (95%CI = 0,49-0,68, p-value = 0,09)

Symptoms and clinical signs

When it comes to symptoms reported by the patients, we noticed that coughing is significantly less prevalent in the LP group (p-value = 0,03). However, the AP group sees a higher prevalence of non-productive cough, but it is only a trend. The absence of chest pain is only significant when comparing the AP to the NAP group (p-value = 0,05), but for the LP and MP groups it remains unsignificant. Confusion is significantly overrepresented in both the AP (p-value < 0,01) and LP groups (p-value < 0,01), while being almost significantly more prevalent also in the MP group (p-value = 0,06). The symptoms of dyspnea and sensation of fever do not significantly differ between groups.

On auscultation, focal signs cannot help to differentiate the etiological pathogen.

For all vital signs measured, only hypoxemia, defined as an oxygen saturation below 90%, has a significant difference between groups, being less prevalent in the LP group (p-value = 0,03). All other vital signs such as heart rate, blood pressure, respiratory rate and temperature do not significantly differ. There was an almost significant trend for a higher temperature being associated with the AP group.

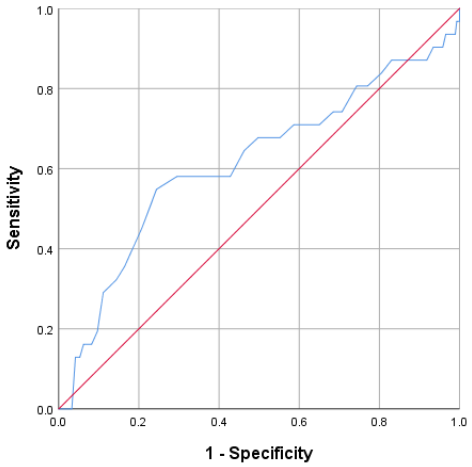

Figure 5 - ROC curve for body temperature, for AP vs. NAP. AUC = 0,62 (95%CI = 0,50-0,73, p-value = 0,06)

Ancillary tests

Hyponatremia is highly predictive of the presence of *L. pneumophila* (p-value < 0,001), the average serum sodium levels in the LP group being below 132 mmol/L. This confirms what has been repeatedly found in the literature, many predictive scores using hyponatremia as a dichotomic variable with a cut-off for example established at 133 mmol/L in the Legionella Score. CRP, a variable only measured in 230 patients, is significantly higher in the AP (p-value = 0,01) and LP (p-value < 0,01) groups. Hyponatremia and high CRP seem therefore to be specific predictive factors of *L. pneumophila,* since they are only significant for the LP group and not the MP group.

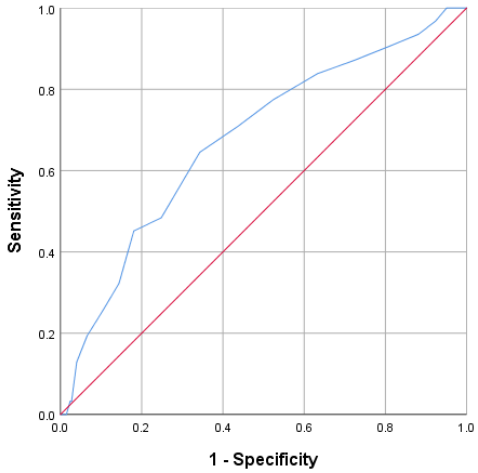

Figure 6 - ROC curve for natremia (decreasing levels), for AP vs. NAP. AUC = 0,68 (95%CI = 0,58-0,78, p-value = 0,001)

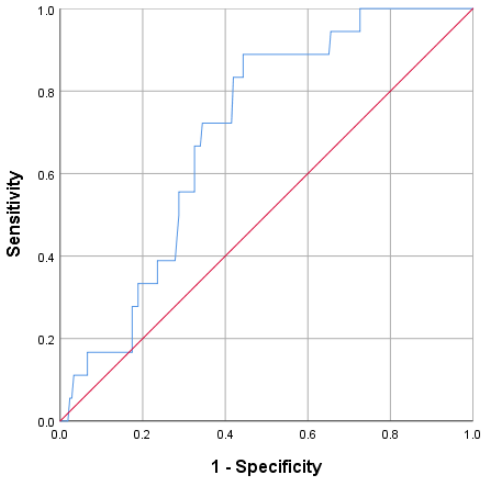

Figure 7 - ROC curve for CRP, for AP vs. NAP. AUC = 0,70 (95%CI = 0,60-0,80, p-value = 0,005)

Moreover, the leucocytes count is lower in the AP group, at the limit of being significant (p-value = 0,08), and is significantly lower in the MP group. Again, this comforts the findings described in the literature and is the only predictive factor that appeats to be specific for *M. pneumoniae*.
Other laboratory variables such as urea, glucose, hematocrit, procalcitonin and platelet count did not significantly differ between groups. This is unfortunate especially for the platelet count that is one of the variables for one of the Legionella score described earlier.
From a radiological point of view, the presence of pleural effusion does not differ between groups.

Scores

The Pneumonia Severity Index (PSI) score cannot help distinguishing atypical pathogens from others. Yet, it is important to keep in mind, that severe CAP cases (PSI class V) were excluded by design. Since LDH were not measured in this study, we cannot attempt a validation of the Legionella Score by Fiumefreddo et al[51].

Comorbidities

From all the comorbidities we tested, only heart failure is significantly more prevalent in the AP group (p-value = 0,03), especially for the LP group (p-value < 0,01), but not the MP group. 50% of our patients with a pneumonia caused by *L. pneumophila* were suffering from heart failure. In the literature, some studies have associated cardiac diseases with a higher risk of having pneumonia being caused by *L. pneumophila*, yet others have described chronic heart failure as a negative predictive factor.
All other comorbidities such as chronic obstructive pulmonary disease (COPD), chronic liver disease, chronic renal disease and active cancer do not significantly differ between the etiological groups. The number of individual comorbidities does not influence the outcome either.
Previous antibiotic use is only reported in the NAP group, but this is not significant.
Alcohol abuse is significantly associated with *L. pneumophila* (p-value = 0,05) which coincides with what has been described in the literature. Unfortunately, smoking was not a measured variable and could therefore not be tested in this cohort.

Exposure

When looking at the seasonal distribution of the different etiologies, there is a significant difference for the AP group (p-value = 0,03). The atypical pathogens and *L. pneumophila* are more prevalent in autumn (p-value = 0,007 and 0,04 respectively). For *M. pneumoniae* this trend can be found again, without being significant (p-value = 0,08). This coincides with the literature stating that *L. pneumophila* is more prevalent in the warm and humid months of summer and early fall[42,130,139] and that *M. pneumoniae* is less prevalent in winter months[73].

All results of the univariate statistical analysis are summarized in Table 10. The p-values in bold letters are considered as significant and the ones underlined are inferior to 0,1 and are therefore also used for the multivariate part of the statistical analysis.

Table 10- Table 10 - Univariate statistical analysis, within parenthesis the standard deviation (continuous variable) or percentage (categorical variable) (1Chi-Square Test, 2Fischer's Exact Test) (color coding: grey = demographical factors, dark blue = symptoms, red = clinical signs, orange = vital signs, green = ancillary tests (laboratory and chest radiography), yellow = scores, light blue = comorbidities, purple = exposure factors)

Variable		AP (N=31)	LP (N=16)	MP (N=15)	NAP (N=549)	P value AP vs NAP	P value LP vs others	P value MP vs others
Age		67 (17)	65 (19)	70 (15)	72 (16)	0,09	0,07	0,58
Gender (male)		19 (61)	12 (75)	7 (47)	314 (57)	0,65	0,15	0,40
Heart failure		11 (36)	8 (50)	3 (20)	105 (19)	**0,03**	**<0,01**	0,98
COPD		5 (16)	3 (19)	2 (13)	117 (21)	0,49	0,82	0,45
Chronic liver disease		1 (3)	1 (6)	0	6 (1)	0,29	0,06	0,66
Active cancer		3 (10)	2 (13)	1 (7)	35 (6)	0,47	0,33	0,94
Chronic renal disease		5 (16)	3 (19)	2 (13)	83 (15)	0,88	0,69	0,81
Diabetes		3 (10)	1 (6)	2 (13)	93 (17)	0,29	0,26	0,73
Neurological disease		5 (16)	1 (6)	4 (27)	61 (11)	0,39	0,51	0,07
Alcohol abuse		5 (16)	4 (25)	1 (7)	54 (10)	0,26	**0,05**	0,66
Number of comorbidities	0	12 (39)	4 (25)	8 (53)	217 (40)	0,63	0,48	0,30
	1	8 (26)	6 (38)	2 (13)	177 (32)			
	>1	11 (36)	6 (38)	5 (33)	155 (28)			
Previous antibiotic		0	0	0	26 (5)	0,22	0,38	0,42
Cough		24 (77)	10 (63)	14 (93)	457 (84)	0,38	**0,03**	0,28
Sputum		15 (48)	7 (44)	8 (53)	326 (60)	0,22	0,21	0,66
Chest pain		5 (17)	3 (20)	2 (13)	187 (34)	**0,05**	0,27	0,11
Dyspnea		22 (73)	10 (67)	12 (80)	383 (70)	0,70	0,76	0,38
Fever		24 (77)	13 (81)	11 (73)	370 (67)	0,25	0,25	0,62
Confusion		5 (16)	3 (19)	2 (13)	17 (3)	**<0,01**	**<0,01**	0,06
Temperature		38,2 (1,3)	38,3 (1,3)	38,0 (1,2)	37,9 (1,0)	0,09	0,08	0,53
Heart rate		99 (20)	105 (23)	92 (12)	98 (20)	0,91	0,18	0,23
Respiratory rate		25 (6)	26 (6)	25 (6)	24 (6)	0,30	0,27	0,71
SBP		135 (17)	131 (13)	140 (20)	133 (24)	0,66	0,69	0,33
DBP		77 (11)	76 (7)	78 (14)	73 (14)	0,19	0,57	0,22
Hypoxemia		12 (40)	4 (25)	8 (57)	279 (52)	0,21	**0,03**	0,67
Focal signs on chest examination		24 (77)	13 (81)	11 (73)	461 (84)	0,33	0,78	0,28
Sodium		133,4 (4)	131,9 (3)	135,1 (4)	135,9 (4)	**<0,01**	**<0,01**	0,52

Urea		7,3 (4)	8,0 (6)	6,7 (3)	7,6 (5)	0,71	0,75	0,43
Glucose		7,6 (2)	7,7 (2)	7,5 (2)	7,6 (3)	0,90	0,96	0,81
Leucocytes count		11,5 (4,3)	12,8 (4,5)	10,2 (3,6)	13,6 (6,4)	0,08	0,66	**0,04**
Hematocrit		39,3 (5)	39,3 (5)	39,3 (5)	39,2 (5)	0,86	0,91	0,93
Platelets count		212,2 (89)	221,4 (94)	202,5 (85)	233,8 (97)	0,23	0,64	0,23
PCT		1,5 (3)	1,4 (2)	1,5 (4)	3,8 (14)	0,37	0,54	0,55
CRP (N=230)		265,6 (112)	333,2 (87)	231,8 (110)	180,4 (138)	**0,01**	**<0,01**	0,23
Pleural effusion		6 (19)	3 (19)	3 (20)	91 (17)	0,69[1]	0,74[2]	0,73[2]
PSI score		86,3 (24)	87,7 (27)	84,9 (22)	84,2 (25)	0,64	0,58	0,94
Season	Winter	5 (16)	2 (13)	3 (20)	207 (38)	**0,03**	0,12	0,22
	Spring	6 (19)	4 (25)	2 (13)	123 (22)			
	Summer	5 (16)	2 (13)	3 (20)	76 (14)			
	Autumn	15 (48)	8 (50)	7 (47)	143 (26)			

Multivariate statistical analysis

As the LP and MP populations were very small (16 and 15 patients respectively), we did only proceed the multivariate analysis for the prediction of the AP group.

For the comparison between the AP and NAP groups, 9 variables had a p-value below 0,01. However, we first decided to exclude the CRP, because it was only measured in 230 patients. Confusion was also excluded, considering the fact that less than 10% of all patients presented this symptom. Therefore, only 7 variables were kept for the multivariate statistical analysis: age, heart failure, chest pain, temperature, autumn, serum sodium and leucocytes count.

After executing the logistic regression with backward conditional selection (Hosmer and Lemeshow Test: 0,30), temperature and leucocytes count were not significant anymore. The final model has therefore only 5 variables, which is adapted to the number of patients in the AP group (1 variable for 6 cases). The final model is summarized in Table 11.

Table 11 – Independent significant variables for AP vs. NAP

Variable	Odds ratio	95% CI	P-value
Age (year)	0,965	0,941-0,990	0,006
Heart failure	2,893	1,196-6,995	0,018
Chest pain	0,251	0,087-0,727	0,011
Autumn	2,637	1,215-5,726	0,014
Sodium (mmol/L)	0,900	0,828-0,979	0,014

From the remaining variables, both the presence of heart failure and contracting pneumonia during autumnal months are independent positive predictive factors for the presence of atypical pathogens. The presence of chest pain, an advanced age and higher serum sodium levels are independent negative predictive factors for the presence of atypical bacteria. In other words, an absence of chest pain, younger age and lower natremia make a pneumonia caused by an atypical pathogen more probable.

In order to have all independent variables dichotomized, a threshold was selected for both continuous variables using the Youden Index: 75 years for the age (Youden Index = 0,17) and 135 mmol/L for natremia (Youden Index = 0,31). Taking these two thresholds into

consideration, a secondary multivariate analysis uncovered slightly different odds ratios and p-values, as shown by Table 12, yet all remain independent predictive factors.

Table 12 - Independent significant variables for AP vs. NAP, after dichotomization

Variable	Odds ratio	95% CI	P-value
Age > 75 years	0,374	0,162-0,863	0,021
Heart failure	2,567	1,089-6,054	0,031
Chest pain	0,333	0,122-0,910	0,032
Autumn	2,708	1,250-5,867	0,012
Sodium ≥ 135 mmol/L	0,336	0,152-0,740	0,007

Establishment of a new predictive score

Because the 5 previously described predictive factors can be detected by taking a simple patient's history and doing a routine laboratory exam, they were incorporated in an easy-to-use predictive score. Each criterion equals either 0 or 1 point and the score equals the sum of all points, for a total ranging between 0 and 5 points. Aiming to make this score as easy to remember as possible, the mnemonic "CASH-75" can be used to easily recall all 5 clinical features. Table 13 summarizes the score.

Table 13 - The "CASH-75" predictive score for atypical bacteria in pneumonia

CASH-75	Clinical feature	Point
C	Absence of **C**hest pain	1
A	Contracting the disease in **A**utumn	1
S	**S**odium < 135 mmol/L	1
H	**H**eart failure	1
75	Age < **75** years	1

The higher the score, the more probable the presence of an atypical bacteria becomes. Applying this score on the BICAP data base, the patients can be classified as shown in Table 14 (2 were excluded, because of an incomplete data set).

Table 14 - Distribution of the patients depending on the etiology and the CASH-75 score

Score	Number of patients		Total
	NAP group	AP group	
0	23	0	23
1	170	0	170
2	207	9	216
3	118	14	132
4	27	7	34
5	3	0	3
Total	548	30	578

At first glance, lower thresholds (≥ 1 and ≥2) seem to be good at excluding atypical pathogens, while the highest cut-off (≥5) seems to be useless, since the only positive cases would be non-atypical pathogens. The performance characteristics of the score were then calculated for each cut-off and summarized in Table 15. The ROC curve was modelized with an AUC of 0,78 (95% CI = 0,71-0,85, p-value < 0,001).

Table 15 - Performances of the CASH-75 score depending on the various cut-offs (PPV = positive predictive value, NPV = negative predictive value, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, DOR = diagnostic odds-ratio)

Cut-off	Sensi (%)	Spe (%)	PPV (%)	NPV (%)	LR+	LR-	DOR
≥ 1	100	4	5	100	1,04	0	+ ∞
≥ 2	100	35	8	100	1,54	0,35	4,4
≥ 3	70	73	12	98	2,59	0,41	6,32
≥ 4	23	94	19	96	3,83	0,82	4,67
≥ 5	0	99	0	95	0	1,01	0

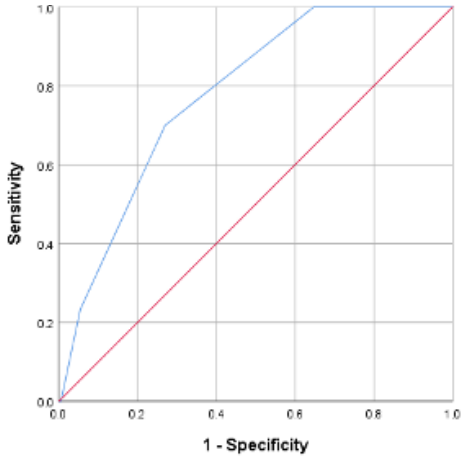

Figure 8 - ROC of the CASH-75 score, for AP vs. NAP, AUC = 0,78 (95%CI = 0,71-0,85, p-value < 0,001)

With a cut-off set at ≥2 for a positive result, a negative test would imply an absence of an atypical pathogen with a sensitivity of 100% and a negative predictive value of 100%. With a cut-off of ≥3, the specificity increases to 73%, the sensitivity decreases to 70%, but the negative predictive value remains seemingly high at 98%. Between these two thresholds, the negative likelihood ratio goes from 0,35 to 0,41 when increasing the cut-off. The higher cut-offs, such as ≥4 and ≥5, are not good enough for confirming the absence of an atypical pathogen, with a sensitivity of respectively 23% and 0%. From a purely mathematical point of view, the cut-off of ≥3 seems to be the most performing with the highest diagnostic odds-ratio (the DOR of the ≥2 cut-off being invalid).

Discussion

The univariate statistical analysis showed that heart failure, confusion, high CRP serum levels and hyponatremia are significant positive predictive factors for atypical pathogens, while the presence of chest pain is a negative predictive factor. Comparing this with our literature review, none of the predictive factors listed above were described for atypical bacteria in general. However, the literature reported that a younger age, a higher body temperature and a lower leucocytes count are associated with the presence of an atypical etiology[19]. While these variables are not significant in the BICAP cohort, the trends can be uncovered here with a p-value inferior to 0,1. Besides, a CAP is in general more frequent in winter, especially because *S. pneumoniae* and respiratory viruses see their prevalence peak during this season, yet atypical pathogen are more prevalent in summer and autumnal months[103], as shown also by this cohort. That is why from a seasonal point of view, contracting the disease in autumn is a positive predictive factor for atypical bacteria.

The multivariate analysis identified that an age under 75, the presence of heart failure, the absence of chest pain, hyponatremia and contracting the disease in autumn are independent positive predictive factors for atypical pathogens.
For *L. pneumophila*, heart failure, alcohol abuse, confusion, high CRP serum levels and hyponatremia are positive predictive factors, yet the presence of cough and hypoxemia are negatively associated. Moreover, contracting a CAP caused by *L. pneumoniae* is more prevalent during autumnal months. The literature seems to partially agree with this seasonal distribution, however most authors describe summer and autumn as the seasons with the highest prevalence[31,43–45,103]. While most of these predictive factors were already described in other studies and therefore confirmed through this data base, heart failure was both depicted as a negative[51,56] and as a positive[101,104] predictive factor. Furthermore, hypoxia[117] was described as associated with the presence of *L. pneumophila*, yet in this study severe pneumonia were also included, since the death rate equals 50%. Other risk factors previously defined by multiple studies such as the absence of sputum[51,98–100,115,116], high PCT levels[56,106], diabetes[42,45,46,49,101,104,123,127,130], the presence[43,54,58,102,113,123,128] or absence[51,56,98–100] of COPD and the presence[52,98,100,102,137] or absence[99] of previous antibiotic use could not be confirmed as significant in this study. The fact that the literature depicts some clinical features both as positive and negative speaks in favor of a weak association. Our study suggests this again by showing that COPD and a previous antibiotic use cannot truly predict the presence of *L. pneumophila*.
When it comes to *M. pneumoniae*, only one clinical feature differs significantly with the rest of CAP and that is a lower leucocytes count. This has only be described in one other study to our knowledge[67]. The literature describes winter as the season with the highest prevalence of this pathogen[151], however this trend is not found in our study, autumn even being almost significantly the most prevalent (p-value = 0,08). Yet, a pediatric study has depicted winter as the season in which *M. pneumoniae* is significantly less frequent than other etiologies[73]. Our patient database could unfortunately not validate other risk factors described by other authors. In general, there is a lack of established predictive factors for this pathogen and our study does not uncover any new one. In comparison to *L. pneumophila*, fewer articles have been published about *M. pneumoniae* apropos adult populations, probably because the latter affects mostly a pediatric population and it is far less deadly than Legionnaire's disease.

Predictive score

With an AUC of 0,78 (95% CI = 0,71-0,85, p-value < 0,001), the accuracy of this CASH-75 score seems to be satisfactory. This is further shown when comparing with other scores used for pneumonia and their performances, such as the CURB-65 score for predicting the mortality at 28 or 30 days which has AUC equaling 0,614 and 0,756 respectively[152,153]. Another way to put the AUC into perspective is comparing it with a score that is currently used in clinical practice, like the revised Geneva score used for diagnosing a pulmonary embolism. A recent meta-analysis revealed that the AUC for this score equals 0,69 (95%CI = 0,65-0,74, p-value < 0,001)[154], which is again inferior to the AUC of the CASH-75 predictive score.
Moreover, the fact that all the information needed to compute this score can be obtained through a basic anamnesis and routine laboratory tests for the serum sodium level is an advantage. Also, all criteria equal only 1 point and there is no ponderation between them. This confers simplicity to this score , when comparing for example with the PSI score which

has 20 different criteria with a ponderated point system, making it very complex to calculate and uneasy to use in a clinical setting[152,153,155].

The main objective of the CASH-75 score is to be able to exclude the presence of an atypical bacteria as the pneumonia's etiology. For this purpose, they are two candidates for the ideal cut-off. The first one, is the threshold ≥2 that has a sensitivity and negative predictive value of 100%, meaning no cases of atypical pathogen would be missed and all of them could be covered by an additional antimicrobial. The second ideal cut-off is ≥3, which has the best diagnostic odds-ratio (DOR) value. Yet, the gain in specificity is opposed by the decrease in sensitivity, implying that some CAP caused by atypical pathogens would not be covered by an adequate antibiotic. On the other hand, 207 cases that were previously false positives would be reclassified as true negatives, thus an overtreatment in more patients would be prevented.

Either way, both cut-offs help hinder a prescription of an additional antibiotic covering an atypical bacteria, before having any microbiological diagnosis. This may lead to less bacterial resistance, less drug side effects and interactions, and a cost reduction. The performance of this score needs undoubtedly further validation from a temporal, geographical and domain point of view[105]. The geographical validation is particularly important, since one of the criteria is the season of contracting pneumonia. Because the score was derived using a cohort of patients only living in Switzerland, the local climate must be taken into consideration in other countries.

Strength and limitations

This study has some strength; it was conducted using a prospective multicentric cohort with thorough assessment of the presence of pneumonia and search for typical and atypical pathogens in all patients, hence minimizing the risks of misclassification.

Nevertheless, some limitations must be recognized. Because of the secondary analysis setting, not all variables of interest described in the literature were available in our patients. For example, the smoker status remained unknown and the LDH were not measured, both being described as significant predictive factors for the presence of *L. pneumophila*. Missing LDH is particularly bothersome, since it is also used in the Legionella score[51] and an attempt to validate this score could therefore not be undertaken. The CRP was also only measured in less than half of all patients (230 out of 580 patients), and while the univariate statistical analysis proved it to be significant for both the AP and LP groups, this variable missing in too many patients disqualified it for the multivariate analysis.

From a purely methodological point of view, the design of the comparison used for the statistical analysis cannot rule out the presence of *L. pneumophila* or *M. pneumoniae* in the NAP group. Indeed, the cases of pneumonia caused by an unknown pathogen were classified in the NAP group, thus there is a possibility of comparing atypical pathogens with other atypical pathogens through this measurement bias. This issue is emphasized by the fact that the *L. pneumophila* diagnosis was established using the urinary antigens; a technique that lacks in sensibility, only detecting serogroup 1 which represents about 80% of all strains[8,14,31,54].

A lot of comparisons were done, and some association between a predictor variable and presence of atypical pathogens could be spurious. Finally, the total number of patients in the AP group was low, and overadjustment of the score is a possibility, reinforcing the need for external validation.

Conclusion

There are independent predictive factors that can predict the presence of an atypical etiology in patients hospitalized for pneumonia. If these findings can be replicated in other cohorts, use of the CASH-75 score could help excluding the presence of atypical bacteria in non-severe CAP using simple, easy to obtain variables. This would enable a more restrictive pattern of prescription of an additional antimicrobial in the treatment of CAP, with beneficial effects on bacterial resistance, drug adverse effects and interactions, while maintaining lower costs.

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