FebriDx®: A Rapid Diagnostic Test for Differentiating Bacterial and Viral Aetiologies in Acute Respiratory Infections

Matt Shirley

Published online: 6 November 2019
© Springer Nature Switzerland AG 2019

Abstract
FebriDx® is a rapid, point-of-care diagnostic test that is designed to aid in the differentiation of bacterial and viral acute respiratory infections (ARIs), thus helping to guide decisions regarding the prescription of antibiotics in the outpatient setting. FebriDx carries a CE mark for use in the EU and is also approved in several other countries, including Canada, Saudi Arabia and Singapore. It is indicated for use in patients > 2 years old with symptoms consistent with a community-acquired ARI. The test involves the use of an immunoassay on a fingerstick blood sample to provide simultaneous, qualitative measurement of elevated levels of C-reactive protein (CRP) and myxovirus resistance protein A (MxA). In two prospective, multicentre studies in patients with acute upper respiratory tract infections, FebriDx was shown to be both sensitive and specific in identifying patients with a clinically significant infection and in differentiating between infections of bacterial and viral aetiology. The test is simple, requires no additional equipment and produces actionable results in ~ 10 min. As was demonstrated in a small, retrospective analysis, FebriDx results can help guide (improve) antibiotic prescribing decisions. Reducing the unnecessary or inappropriate prescription of antibiotics for ARIs of probable viral aetiology is important for antibiotic stewardship and can also reduce the unnecessary exposure of patients to the risk of antibiotic-related adverse events. FebriDx thus represents a useful diagnostic tool in the outpatient setting.

1 Introduction
Acute respiratory infections (ARIs), which can be viral or bacterial, are one of the most common reasons for visits to primary and urgent care clinics [1]. Given their overlapping profiles of signs and symptoms, distinguishing between ARIs of bacterial and viral aetiology can be clinically challenging [2]. Clinical uncertainty regarding the infection aetiology, along with other factors (e.g. patient or parental pressure or expectations [3]), frequently results in the prescription of antibiotics for infections of probable viral aetiology despite no likely benefit [4–6]. The unnecessary or inappropriate prescription of antibiotics can have broad negative consequences, including contributing to the rise and spread of antimicrobial resistance (itself considered one of the biggest threats to global health) [7, 8] and unnecessarily exposing the patient to the risk of adverse events (including life-threatening events, e.g. anaphylaxis, Stevens-Johnson...
syndrome, Clostridium difficile infection) [9–11]. As well as negatively affecting patient health and care (at both the individual and population level), these effects are also associated with significant economic costs [12–14].

Sensitive and specific diagnostic tools to aid in the diagnosis of ARIs (particularly in differentiating bacterial and viral infections) in primary and urgent healthcare settings have been lacking [2, 15]. Available methods, such as standalone C-reactive protein (CRP) measurement, procalcitonin measurement, and molecular (e.g. rapid antigen detection testing, PCR) and culturing methods are limited by issues including insufficient sensitivity and/or specificity (including an inability to distinguish between colonization and a true infection), excessive time for results to provide actionable data, poor reproducibility and/or a requirement for specialized (and potentially costly) equipment [2, 15].

FebriDx® is a rapid, point-of-care diagnostic test that is designed to aid in the differentiation of bacterial and viral ARIs, with the objective of helping to reduce the inappropriate prescription of antibiotics for ARIs of viral aetiology [16]. The test (which carries a CE mark and is undergoing FDA trials for approval) involves the use of an immunosay on a fingerstick blood sample to provide simultaneous, qualitative measurements of CRP and myxovirus resistance protein A (MxA) which, together, can be used (in conjunction with clinical assessment) to identify patients with a clinically significant infection and to distinguish between infections of bacterial and viral aetiology [16]. This article reviews the FebriDx test technology, clinical performance and utility for its intended use under the CE mark based on available data.

2 Indications for Use

FebriDx carries a CE mark and is approved for use in the EU and all countries recognizing the mark [17]. FebriDx is also commercially available in Australia, Canada, Singapore and in countries of the Gulf Cooperation Council (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and the United Arab Emirates) [18].

FebriDx is intended for use by medical professionals in an outpatient setting (i.e. by primary care/general practitioners as well as in urgent care/out-of-hours medical centres, pharmacies and emergency departments) [19]. The test is indicated for use in aiding the diagnosis of an ARI in patients > 2 years old who present within 3 days of an acute-onset fever and within 7 days of new onset respiratory symptoms consistent with a community-acquired ARI, including possible cough and/or acute bronchitis. Specifically, FebriDx is designed for use in differentiating between viral (influenza A/B, adenovirus, respiratory syncytial virus, metapneumovirus, parainfluenza virus or Epstein–Barr virus) and bacterial ARIs. A negative FebriDx test result does not preclude a respiratory infection (e.g. one caused by rhinovirus or coronaviruses); the test should be used in conjunction with other clinical evidence, including laboratory, radiographic and epidemiological information [19].

3 FebriDx Technology

The FebriDx test is an immunoassay that utilizes simultaneous, qualitative measurement of CRP and MxA in peripheral whole blood [16]. CRP is a non-specific acute-phase protein that serves as a sensitive and early marker of inflammation, tissue injury or infection [20–23]. CRP levels become markedly elevated in the presence of a clinically significant acute bacterial infection and, as such, CRP measurement can play a role in the diagnosis of such infections; however, CRP is not considered to be sufficiently specific as a marker on its own to differentiate between bacterial and viral infections [20–26]. MxA is an intracellular GTPase protein that is induced by type I and type III interferons [27] and which serves as a sensitive and specific marker for viral infection [28–32]. MxA has antiviral activity against a broad range of pathogenic viruses, and interferon production in response to viral infection leads to an increase in MxA levels [27]. The rationale behind the FebriDx test is that through measurement of CRP and MxA together, it can combine the sensitivity of CRP with the specificity of MxA such that, when used together in a rapid point-of-care test, these markers can serve to aid in the differentiation between viral and bacterial ARIs [16].

The all-in-one, single-use, disposable FebriDx test device consists of a lateral flow test strip, together with a built-in safety lancet, a blood collection tube and a buffer delivery system, all contained in a plastic housing unit [19]. The test strip contains two result lines, one for CRP and one for MxA (with monoclonal anti-CRP and anti-MxA antibodies, respectively), and a control line [16]. The FebriDx test produces visual, qualitative results—if the serum level of CRP and/or MxA meets the cut-off level (i.e. ≥ 20 mg/L for CRP and ≥ 40 ng/mL for MxA), a corresponding (positive) line will appear in the results window [16, 19]. These cut-off levels were selected to optimize the sensitivity and specificity of the combination to differentiate between viral and bacterial ARIs [33]. Whereas patients with ARI symptoms and a CRP level < 20 mg/L are likely to have a non-bacterial and/or self-limiting infection, CRP levels ≥ 20 mg/L are associated with a clinically significant immune response; an MxA level ≥ 40 ng/mL was established as a sensitive cut-off for identifying viral infections [33–35].

The FebriDx test procedure is simple and rapid (typically performed in < 30 s) [16, 19]. Briefly, the fingertip is lanced using the built-in lancet; the blood sample (~ 5 μL) is drawn
within the past 3 days [34, 35]. Patients suspected of having a lower respiratory tract infection (other than acute bronchitis) were excluded. Among enrolled patients in the two studies, 56 (27.3%) of 205 patients [34] and 13 (5.9%) of 220 [35] patients were aged < 18 years.

In each study, patients underwent testing both with FebriDx and with a panel of reference diagnostic tests that were designed to identify patients with clinical significant ARIs and to differentiate between bacterial and viral aetiologies [34, 35]. The reference diagnostic tests included standardized microbiological tests (e.g. bacterial culture, PCR for viral and atypical bacterial pathogens) to detect bacterial and/or viral pathogen presence, and laboratory tests [e.g. white blood cell count (including checks for lymphocytosis and bandaemia), measurement of serum procalcitonin level, Epstein–Barr virus serology] to identify any host immune response. An algorithm based on the reference testing data was used to classify patients. Under both the FebriDx testing and the reference testing algorithm, patients were classified as a having a bacterial ARI, a viral ARI, or negative for a clinically significant ARI. Additionally, a panel of two physicians with expertise in respiratory infections, and who were blinded to the FebriDx test results, reviewed each individual patient case report together with the reference testing results and could overrule the reference testing algorithm classification to give the final reference classification [34, 35].

The reference algorithm classified 12.2 and 15.5% of patients in the two studies as bacterial, 25.9 and 56.4% as viral and 62.0 and 28.2% as negative [34, 35]. In both studies there was strong (99%) agreement between the physician panel and the algorithm classifications. Two patients in the first study and one patient in the second study who were classified as negative by the reference algorithm were reclassified by the physician panel as bacterial. Based on the FebriDx test results, 15.6 and 19.1% of patients in the two studies were classified as bacterial, 35.1 and 60.9% as viral and 49.3 and 20.0% as negative [34, 35].

The FebriDx test demonstrated a high degree of diagnostic accuracy for identifying patients with clinically significant bacterial and viral ARIs (Table 1). When classifying results as bacterial versus not bacterial, overall agreement between the FebriDx result and the reference standard result with physician override was 92% in both studies; when classifying results as viral versus not viral, overall agreement was 84–87% [34, 35]. Across the studies, bacterial infection sensitivities and specificities were 80–85% and 93–94%, respectively, and viral sensitivities and specificities were 87–90% and 76–84%, respectively (Table 1). Of note, the accuracy of FebriDx in diagnosing bacterial infection was enhanced in patients confirmed to have a fever at the time of enrolment, with the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in both studies all higher among these patients compared with the overall study populations (Table 1) [34, 35].

In a further test of FebriDx specificity, one of the studies also included an asymptomatic control population (n = 165 in total, 163 analysed; 158/163 aged ≥ 18 years) from a convenience sample of subjects without any signs or symptoms of infection [34]. Among this asymptomatic control population, 161 of 163 subjects had a negative FebriDx test result, giving a test specificity of 99% (95% CI 96–100%). There were two (1.2%) false positive FebriDx test results, one viral and one bacterial, both of which were confirmed by ELISA testing to be accurate measurements of MxA and CRP, respectively. Additionally, there was one subject who tested FebriDx negative who was found to have an elevated CRP level [34].

4 Clinical Performance of FebriDx

The clinical performance of the FebriDx test has been evaluated in two prospective multicentre clinical trials, which each used a convenience sample of patients enrolled at 10 clinical sites in the USA [34, 35]. In both studies, enrolled patients were adults or children aged > 1 year with clinical signs and symptoms of an acute upper respiratory tract infection (including a new onset of cough or sore throat within the past 7 days) and a history of fever (≥ 100.5 °F/38.1 °C) within the past 3 days [34, 35]. Patients suspected of having a lower respiratory tract infection (other than acute bronchitis) were excluded. Among enrolled patients in the two studies, 56 (27.3%) of 205 patients [34] and 13 (5.9%) of 220 [35] patients were aged < 18 years.

In each study, patients underwent testing both with FebriDx and with a panel of reference diagnostic tests that were designed to identify patients with clinical significant ARIs and to differentiate between bacterial and viral aetiologies [34, 35]. The reference diagnostic tests included standardized microbiological tests (e.g. bacterial culture, PCR for viral and atypical bacterial pathogens) to detect bacterial and/or viral pathogen presence, and laboratory tests [e.g. white blood cell count (including checks for lymphocytosis and bandaemia), measurement of serum procalcitonin level, Epstein–Barr virus serology] to identify any host immune response. An algorithm based on the reference testing data was used to classify patients. Under both the FebriDx testing and the reference testing algorithm, patients were classified as a having a bacterial ARI, a viral ARI, or negative for a clinically significant ARI. Additionally, a panel of two physicians with expertise in respiratory infections, and who were blinded to the FebriDx test results, reviewed each individual patient case report together with the reference testing results and could overrule the reference testing algorithm classification to give the final reference classification [34, 35].
Evidence for the clinical utility of FebriDx is available from a retrospective chart review analysis involving 21 patients who were administered the FebriDx test after presenting to an outpatient general practice with symptoms of an ARI [39]. The patients were all from a single practice in the UK and had a mean age of 46.3 years (range, 3–84 years). The analysis involved a chart review (for each patient) of the suspected clinical diagnosis, the FebriDx test result, antibiotic prescriptions (including possible management alterations), and the response to therapy and patient outcome [39].

Based on the analysis, the FebriDx test altered the clinical management in 10 (48%) of the 21 cases [39]. These included eight cases where antibiotics were withheld when the FebriDx test indicated a viral infection (six cases) or a negative result (two cases) after a clinical diagnosis of a possible bacterial infection, and two cases where antibiotics were prescribed when the FebriDx test indicated a bacterial infection after a clinical diagnosis of a probable viral infection; one of these two patients was subsequently diagnosed with bacterial sepsis and hospitalized. Additionally, there were two higher-risk patients (a 3-year-old patient with sudden physical deterioration and a 60-year-old immunocompromised patient) who were prescribed antibiotics despite a negative FebriDx test result [39].

All patients in the analysis achieved a full clinical recovery [39]. Excluding the patient who was diagnosed with bacterial sepsis after testing positive for bacterial infection by FebriDx, no patient experienced any clinical complications or required any further unscheduled medical consultations [39].

### Current Status of FebriDx

Advancement in diagnostic testing has been identified as a key area of potential to aid antibiotic stewardship efforts [2, 40]. ARIs account for a large proportion of antibiotic prescriptions in the outpatient setting. However, methods for differentiating ARIs of viral and bacterial aetiology (and thus identifying patients who may benefit from antibiotics) have been limited by issues including insufficient accuracy, excessive time for (actionable) results and/or a requirement for specialized equipment or expertise.

UK National Institute for Health and Care Excellence (NICE) guidelines for the diagnosis and management of pneumonia recommend that point-of-care CRP testing be...
considered for patients presenting with symptoms of lower respiratory tract infection when, after clinical assessment, it is uncertain whether antibiotics should be prescribed [41]. The qualitative FebriDx test measures elevated levels of CRP while simultaneously measuring elevated levels of the viral infection marker MxA together in a simple, rapid, all-in-one, point-of-care test (Sect. 3). The use of the two markers in FebriDx combines the sensitivity of CRP with the specificity of MxA such that, in combination, they can be used to distinguish between viral and bacterial ARIs. Indeed, the clinical performance of the FebriDx test in identifying patients with bacterial ARIs in the outpatient setting was favourable when compared with stand-alone CRP (20 mg/L) or procalcitonin (0.25 ng/mL) qualitative measurement [35]. Furthermore, in indirect comparisons with a diagnostic assay using a combination of CRP, tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) and interferon gamma induced protein-10 (IP-10) measurement [42–44], FebriDx appeared to have similar clinical performance but with the advantages of greater ease of use and more rapid (actionable) results [35]. Another benefit of the FebriDx test is that, unlike pathogen-specific diagnostic tools (e.g. pathogen-specific PCR-based methods), measurement of CRP and MxA (each a component of the body’s immune response) enables FebriDx to distinguish between an infection and the presence of a pathogen in a carrier/colonization state [34, 35].

Based on two prospective, multicentre studies in patients with ARIs (predominantly upper respiratory tract infections, but including patients with acute bronchitis), FebriDx has been shown to be both sensitive and specific in differentiating between infections of viral and bacterial aetiologies (Sect. 4). Of note, the accuracy of the test appeared to be highest when used on patients with confirmed fever at the time of testing. FebriDx is not able to identify patients with a viral and bacterial co-infection (with a host response to both infections); however, such cases appear to be rare (Sect. 3). When defined as the presence of both a viral and a bacterial pathogen (confirmed by PCR and/or bacterial culture) together with a host response inclusive of elevated procalcitonin (≥ 0.25 ng/mL) and/or white blood cell count (≥ 12,000/μL), viral and bacterial co-infection was not observed in the two key trials [34, 35]. Importantly, the FebriDx test was shown to rule out the presence of a clinically significant bacterial infection with a high degree of accuracy (NPV for bacterial infection was 97% in both studies and was 99–100% in patients with confirmed fever at enrolment), suggesting that FebriDx can be used to support the use of a watchful waiting strategy in appropriate cases. The two trials were generally well designed; however, there were some limitations to the data [34, 35]. Most notable of these was the relatively low proportion of paediatric patients (aged < 18 years) included in the trials (16% overall). Given that paediatric patients compose a large proportion of primary care visits for ARIs, further evaluation of the clinical performance of FebriDx in paediatric patients would be of strong interest. Another limitation of the available data is that due to practical constraints, the study populations in the key trials were convenience samples rather than consecutive eligible patients, which potentially could have resulted in a sampling bias.

Complementary to the data regarding the clinical performance of FebriDx, there is some evidence of the clinical utility of FebriDx in reducing unnecessary or inappropriate prescription of antibiotics (Sect. 5). Besides its high level of accuracy, another key benefit of FebriDx is its ability to provide rapid, actionable results at point-of-care which can be used to aid clinical management decisions. Based on a small retrospective outcome analysis, use of FebriDx resulted in a reduction in unnecessary antibiotic prescriptions with no subsequent testing-related adverse events observed (Sect. 5). Accepting the limitations of this small retrospective study (which involved 21 patients from a single practice in the UK), this analysis demonstrated the potential utility of FebriDx in improving the clinical management of patients with ARIs. While clinical uncertainty can lead to the unnecessary or inappropriate prescription of antibiotics for ARIs that are self-limiting and/or of likely viral aetiology [45], use of an accurate diagnostic test at point-of-care to complement clinical judgement may give clinicians more confidence to follow a watchful waiting strategy when appropriate by identifying a low likelihood of a bacterial infection. Furthermore, the availability of clear, simple, visual results (as FebriDx produces) could potentially be used to alleviate patient or parental pressure to prescribe antibiotics when they are not considered necessary. Another aspect of the clinical utility of FebriDx is its potential (through the reduction of unnecessary antibiotics) to reduce the occurrence of antibiotic-related adverse events.

An important factor towards determining the utility of FebriDx in the outpatient setting will be the cost-effectiveness of the test. The costs of the test could be offset (at least partially) by savings on the cost of reducing unnecessary prescriptions. Reductions in medical consultations and treatment of antibiotic-related adverse events could result in more significant cost savings [12]. Furthermore, effects from antibiotic resistance issues are estimated to cost billions of dollars per year globally [46], highlighting the importance of antibiotic stewardship efforts from an economic point of view.

In conclusion, FebriDx represents a sensitive and specific diagnostic tool for aiding in the differentiation between viral and bacterial ARIs. It has the benefits of providing rapid, actionable results from point-of-care testing in a simple-to-use, all-in-one device with no requirements for additional equipment. Further evaluation of the accuracy of the test in paediatric patients and further cost-effectiveness data would
be of interest. However, currently available data suggest that FebriDx is a valuable tool to aid in the diagnosis of ARIs in the outpatient setting, including for use in the identification of patients who might benefit from antibiotics.

| Data Selection—FebriDx*: 96 records identified |
|-----------------------------------------------|
| Duplicates removed | 5 |
| Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial) | 13 |
| Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials) | 32 |
| Cited clinical performance/utility articles | 3 |
| Cited articles not clinical performance/utility | 43 |

Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were: FebriDx, RPS Diagnostics, point-of-care, POC, rapid. Records were limited to those in English language. Searches last updated 30 September 2019.

Acknowledgements  During the peer review process, the manufacturer of FebriDx was also offered an opportunity to review this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Compliance with Ethical Standards

Funding  The preparation of this review was not supported by any external funding.

Conflict of interest  Matt Shirley is a salaried employee of Adis International Ltd/Springer Nature, is responsible for the article content and declares no relevant conflicts of interest.

References

1. Renati S, Linder JA. Necessity of office visits for acute respiratory infections in primary care. Fam Pract. 2016;33(3):312–7.
2. Caliendo AM, Gilbert DN, Ginocchio CC, et al. Better tests, better care: improved diagnostics for infectious diseases. Clin Infect Dis. 2013;57(Suppl 3):S139–70.
3. Cole A. GPs feel pressurised to prescribe unnecessary antibiotics, survey finds. BMJ. 2014;349:g5238.
4. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. JAMA. 2016;315(17):1864–73.
5. Gulliford MC, Dregan A, Moore MV, et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. BMJ Open. 2014;4(10):e006245.
6. Harbarth S, Samore MH. Antimicrobial resistance determinants and future control. Emerg Infect Dis. 2005;11(6):794–801.
7. van de Sande-Bruinsma N, Grundmann H, Verloo D, et al. Antimicrobial drug use and resistance in Europe. Emerg Infect Dis. 2008;14(11):1722–30.
8. World Health Organization. Antibiotic resistance; 2018. http://www.who.int/en/news-room/fact-sheets/detail/antibiotic-resistance. Accessed 20 Sep 2019.
9. Shehab N, Patel PR, Srinivasan A, et al. Emergency department visits for antibiotic-associated adverse events. Clin Infect Dis. 2008;47(6):735–43.
10. Tandan M, Vellinga A, Bruyndonckx R, et al. Adverse effects of amoxicillin for acute lower respiratory tract infection in primary care: secondary and subgroup analysis of a randomised clinical trial. Antibiotics. 2017;6(4):36.
11. US Centers for Disease Control and Prevention. Antibiotic use in the United States, 2017: progress and opportunities; 2017. http://www.cdc.gov/antibiotic-use/stewardship-report/pdf/stewardship-report.pdf. Accessed 20 Sep 2019.
12. Beck JN, Suppes SL, Smith CR, et al. Cost and potential avoidability of antibiotic-associated adverse drug reactions in children. J Pediatr Infect Dis Soc. 2019;8(1):66–8.
13. McGowan JE Jr. Economic impact of antimicrobial resistance. Emerg Infect Dis. 2001;7(2):286–92.
14. Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. Clin Infect Dis. 2003;36(11):1433–7.
15. Rodrigues CMC, Groves H. Community-acquired pneumonia in children: the challenges of microbiological diagnosis. J Clin Microbiol. 2018;56(3):article e01318-17, 1–9.
16. RPS Diagnostics. FebriDx®: product brochure; 2018. http://www.rpsdetectors.com/wp-content/uploads/2018/11/FRM-MKT-361.5_FebriDx-Brochure_Final.pdf. Accessed 20 Sep 2019.
17. RPS Diagnostics. FebriDx® receives updated CE mark to allow incorporation of all-in-one test format [media release]. 31 Oct 2018. http://www.rpsdetectors.com/wp-content/uploads/2018/10/18-1031_FebriDx_NewFormat_CE-Mark.pdf.
18. RPS Diagnostics. FebriDx®; 2019. http://febrix.com. Accessed 20 Sep 2019.
19. RPS Diagnostics. FebriDx®: quick reference guide; 2018. http://www.rpsdetectors.com/wp-content/uploads/2018/11/AP0067.1_FebriDxQuickReference-Guide_Final.pdf. Accessed 20 Sep 2019.
20. Okamura JM, Miyagi JM, Terada K, et al. Potential clinical applications of C-reactive protein. J Clin Lab Anal. 1990;4(3):231–5.
21. Young B, Gleeson M, Cripps AW. C-reactive protein: a critical review. Pathology. 1991;23(2):118–24.
22. Pepys MB, Hirschfeld GM. C-reactive protein: a critical update. J Clin Investig. 2003;111(12):1805–12.
23. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Front Immunol. 2018;9:754.
24. Bray C, Bell LN, Liang H, et al. Erythrocyte sedimentation rate and C-reactive protein measurements and their relevance in clinical medicine. WMJ. 2016;115(6):317–21.
25. Falk G, Fahey T. C-reactive protein and community-acquired pneumonia in ambulatory care: systematic review of diagnostic accuracy studies. Fam Pract. 2009;26(1):10–21.
26. Le Bel J, Hausfater P, Chenevier-Gobeaux C, et al. Diagnostic accuracy of C-reactive protein and procalcitonin in suspected community-acquired pneumonia adults visiting emergency department and having a systematic thoracic CT scan. Crit Care. 2015;19(366):1–12.
27. Haller O, Kochs G. Human MxA protein: an interferon-induced dynamin-like GTPase with broad antiviral activity. J Interferon Cytokine Res. 2011;31(1):79–87.
28. Chieux V, Hober D, Chehadeh W, et al. MxA protein in capillary blood of children with viral infections. J Med Virol. 1999;59(4):547–51.
29. Engelmann I, Dubos F, Lobert P-E, et al. Diagnosis of viral infections using myxovirus resistance protein A (MxA). Pediatrics. 2015;135(4):e985–93.
30. Halminen M, Ilonen J, Julkunen I, et al. Expression of MxA protein in blood lymphocytes discriminates between viral and bacterial infections in febrile children. Pediatr Res. 1997;41(5):647–50.
31. Nakabayashi M, Adachi Y, Itazawa T, et al. MxA-based recognition of viral illness in febrile children by a whole blood assay. Pediatr Res. 2006;60(6):770–4.
32. Zav’yalov VP, Hämäläinen-Laanaya H, Korpela TK, et al. Interferon-inducible myxovirus resistance proteins: potential biomarkers for differentiating viral from bacterial infections. Clin Chem. 2019;65(6):739–50.
33. Sambursky R, Shapiro N. Evaluation of a combined MxA and CRP point-of-care immunoassay to identify viral and/or bacterial immune response in patients with acute febrile respiratory infection. Eur Clin Respir J. 2015;2:28245.
34. Self WH, Rosen J, Sharp SC, et al. Diagnostic accuracy of FebriDx: a rapid test to detect immune responses to viral and bacterial upper respiratory infections. J Clin Med. 2017;6(10):1–16.
35. Shapiro NL, Self WH, Rosen J, et al. A prospective, multi-centre US clinical trial to determine accuracy of FebriDx point-of-care testing for acute upper respiratory infections with and without a confirmed fever. Ann Med. 2018;50(5):420–9.
36. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373(5):415–27.
37. Lingard H, Zehetmayer S, Maier M. Bacterial superinfection in upper respiratory tract infections estimated by increases in CRP values: a diagnostic follow-up in primary care. Scand J Prim Health Care. 2008;26(4):211–5.
38. Mäkelä MJ, Puhakka T, Ruuskanen O, et al. Viruses and bacteria in the etiology of the common cold. J Clin Microbiol. 1998;36(2):539–42.
39. Davidson M. FebriDx point-of-care testing to guide antibiotic therapy for acute respiratory tract infection in UK primary care: a retrospective outcome analysis. J Infect Dis Prev Med. 2017;5(3):1000165.
40. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44(2):159–77.
41. National Institute for Health and Care Excellence (NICE). Pneumonia in adults: diagnosis and management; 2014. http://www.nice.org.uk/guidance/cg191. Accessed 20 Sep 2019.
42. Srugo I, Klein A, Stein M, et al. Validation of a novel assay to distinguish bacterial and viral infections. Pediatrics. 2017. https://doi.org/10.1542/peds.2016-3453.
43. Stein M, Lipman-Arens S, Oved K, et al. A novel host-protein assay outperforms routine parameters for distinguishing between bacterial and viral lower respiratory tract infections. Diagn Microbiol Infect Dis. 2018;90(3):206–13.
44. van Houten CB, de Groot JAH, Klein A, et al. A host-protein based assay to differentiate between bacterial and viral infections in preschool children (OPPORTUNITY): a double-blind, multicentre, validation study. Lancet Infect Dis. 2017;17(4):431–40.
45. Harris AM, Hicks LA, Qaseem A. Appropriate antibiotic use for acute respiratory tract infection in adults: advice for high-value care from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med. 2016;164(6):425–34.
46. Hofer U. The cost of antimicrobial resistance. Nat Rev Microbiol. 2019;17(1):3.